A Dissertation on

BLOOD NEUTROPHIL TO LYMPHOCYTE COUNT AS A PROGNOSTIC MARKER IN LIVER CIRRHOSIS

Dissertation Submitted to

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY CHENNAI - 600 032

With partial fulfillment of the regulations for the award of the degree of

M.D.

GENERAL MEDICINE

BRANCH-I

COIMBATORE MEDICAL COLLEGE, COIMBATORE

APRIL 2017

CERTIFICATE

Certified that this is the bonafide dissertation done by ***Dr. K.S.DAKSHINAMOORTHY*** *and submitted in partial fulfillment of the requirements for the Degree of* ***M.D.,General Medicine,*** *Branch I of* ***The Tamilnadu DR. M.G.R.Medical University Chennai.***

Date:

Guide, Professor & Chief

Prof. DR.S.USHA,MD.

Date:

Professor & Head,
Department of Medicine
Dr. Kumar Natarajan, MD

Date:

Dean

Coimbatore Medical College

Coimbatore

Coimbatore Medical College

COIMBATORE, TAMILNADU, INDIA - 641 014

(Affiliated to The Tamilnadu Dr. MGR Medical University, Chennai)

ETHICS COMMITTEE

CERTIFICATE

Name of the Candidate : DR. DAKSHINAMOORTHY. K.S

Course : M.D. GENERAL MEDICINE

Period of Study : 2014 - 2017

College : COIMBATORE MEDICAL COLLEGE

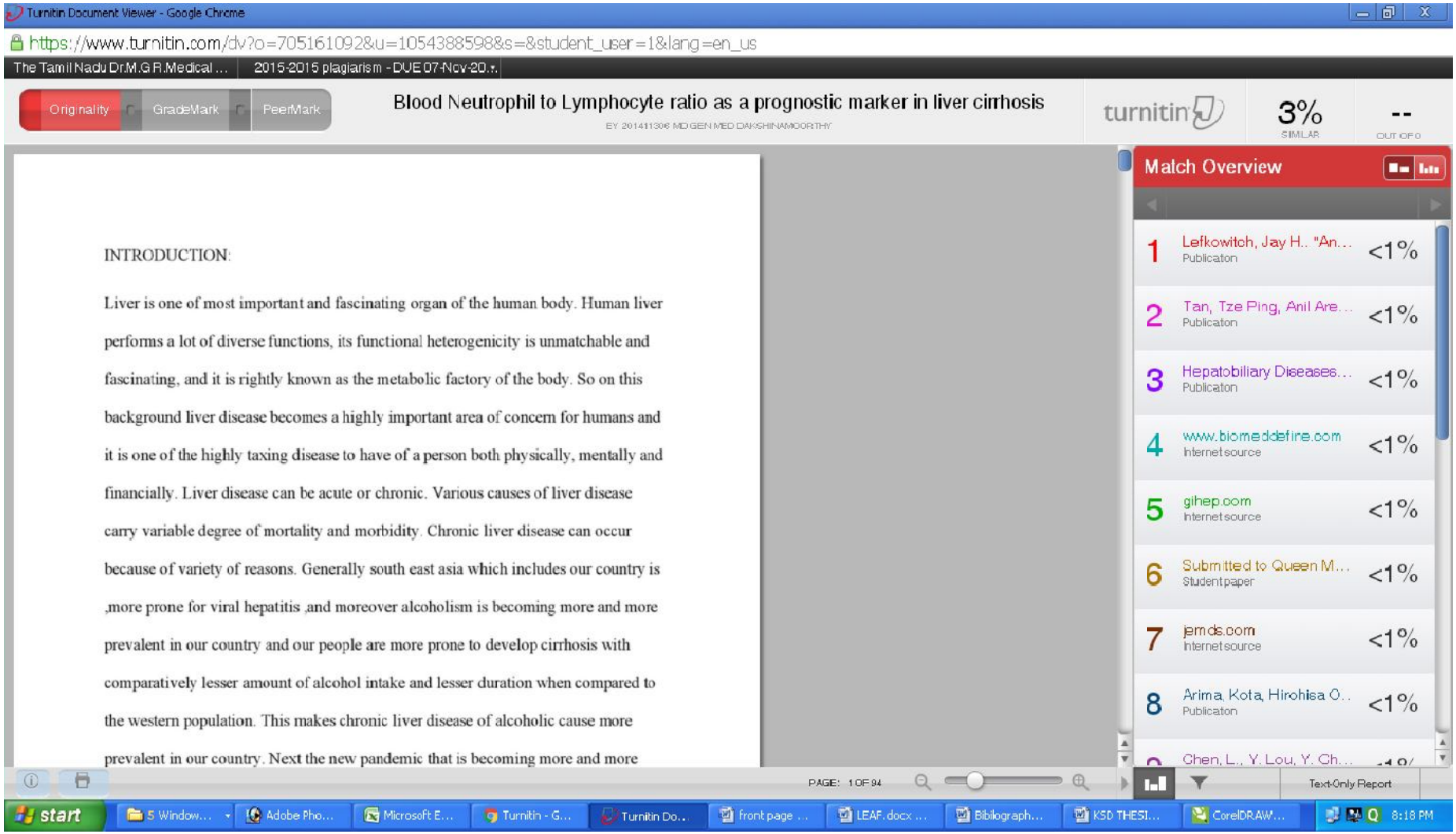
Dissertation Topic : BLOOD NEUTROPHIL TO LYMPHOCYTE RATIO AS A PROGNOSTIC MARKER IN LIVER CIRRHOSIS.

The Ethics Committee, Coimbatore Medical College has decided to inform that your Dissertation Proposal is accepted / ~~Not~~ accepted and you are permitted / ~~Not~~ permitted to proceed with the above Study.

DEAN

Coimbatore Medical College & Hospital, Coimbatore

15. 7. 2015

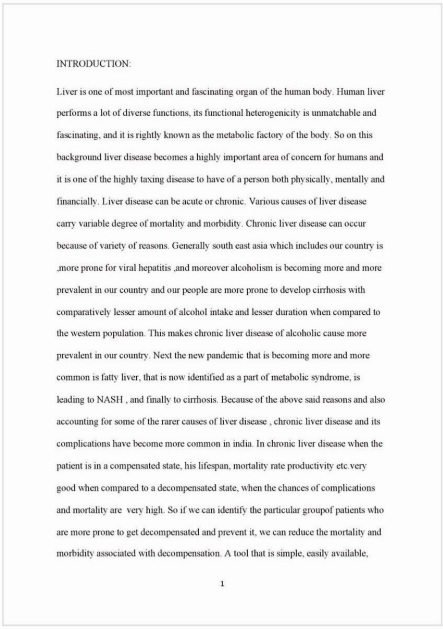

Turnitin Document Viewer - Google Chrome
https://www.turnitin.com/dv?o=705161092&u=1054388598&s=&student_user=1&lang=en_us
The Tamil Nadu Dr.M.G.R.Medical ...
2015-2015 plagiarism - DUE 07-Nov-20...
Originality
GradeMark
PeerMark
Blood Neutrophil to Lymphocyte ratio as a prognostic marker in liver cirrhosis
BY 201411306 MD GEN MED DAKSHINAMOORTHY
turnitin
3%
SIMILAR
--
OUT OF 0
INTRODUCTION:
Liver is one of most important and fascinating organ of the human body. Human liver performs a lot of diverse functions, its functional heterogenicity is unmatchable and fascinating, and it is rightly known as the metabolic factory of the body. So on this background liver disease becomes a highly important area of concern for humans and it is one of the highly taxing disease to have of a person both physically, mentally and financially. Liver disease can be acute or chronic. Various causes of liver disease carry variable degree of mortality and morbidity. Chronic liver disease can occur because of variety of reasons. Generally south east asia which includes our country is ,more prone for viral hepatitis ,and moreover alcoholism is becoming more and more prevalent in our country and our people are more prone to develop cirrhosis with comparatively lesser amount of alcohol intake and lesser duration when compared to the western population. This makes chronic liver disease of alcoholic cause more prevalent in our country. Next the new pandemic that is becoming more and more
Match Overview
1 Lefkowitch, Jay H.. "An... Publicaton <1%
2 Tan, Tze Ping, Anil Are... Publicaton <1%
3 Hepatobiliary Diseases... Publicaton <1%
4 www.biomeddefire.com Internet source <1%
5 gihep.com Internet source <1%
6 Submitted to Queen M... Student paper <1%
7 jemds.com Internet source <1%
8 Arima, Kota, Hirohisa O.. Publicaton <1%
Chen, L., Y. Lou, Y. Ch...
PAGE: 1 OF 94
Text-Only Report
start
5 Window...
Adobe Pho...
Microsoft E...
Turnitin - G...
Turnitin Do...
front page ...
LEAF.docx ...
Bibliograph...
KSD THESI...
CorelDRAW...
8:18 PM

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	201411306 Md Gen Med Dakshinam .
Assignment title:	2015-2015 plagiarism
Submission title:	Blood Neutrophil to Lymphocyte ra …
File name:	KSD_THESIS.docx
File size:	10.66M
Page count:	94
Word count:	12,011
Character count:	67,032
Submission date:	23-Sep-2016 03:58PM
Submission ID:	705161092



INTRODUCTION:

Liver is one of most important and fascinating organ of the human body. Human liver performs a lot of diverse functions, its functional heterogenicity is unmatchable and fascinating, and it is rightly known as the metabolic factory of the body. So on this background liver disease becomes a highly important area of concern for humans and it is one of the highly taxing disease to have of a person both physically, mentally and financially. Liver disease can be acute or chronic. Various causes of liver disease carry variable degree of mortality and morbidity. Chronic liver disease can occur because of variety of reasons. Generally south east asia which includes our country is ,more prone for viral hepatitis ,and moreover alcoholism is becoming more and more prevalent in our country and our people are more prone to develop cirrhosis with comparatively lesser amount of alcohol intake and lesser duration when compared to the western population. This makes chronic liver disease of alcoholic cause more prevalent in our country. Next the new pandemic that is becoming more and more common is fatty liver, that is now identified as a part of metabolic syndrome, is leading to NASH , and finally to cirrhosis. Because of the above said reasons and also accounting for some of the rarer causes of liver disease , chronic liver disease and its complications have become more common in india. In chronic liver disease when the patient is in a compensated state, his lifespan, mortality rate productivity etc very good when compared to a decompensated state, when the chances of complications and mortality are very high. So if we can identify the particular groupof patients who are more prone to get decompensated and prevent it, we can reduce the mortality and morbidity associated with decompensation. A tool that is simple, easily available,

1

DECLARATION

I solemnly declare that the dissertation titled **"Blood Neutrophil to lymphocyte count as a prognostic marker in Liver cirrhosis"** Was done by me from JULY 2015 to JUNE 2016 under the guidance and supervision of **PROF.DR.S.USHA, MD.** This dissertation is submitted to **The Tamilnadu Dr.M.G.R. Medical University** towards the partial fulfillment of the requirement for the award of MD Degree in General Medicine (Branch I).

Dr.K.S.DAKSHINAMOORTHY.

Place:Coimbatore

Date:

ACKNOWLEDGEMENT

I wish to express my sincere thanks to our respected **Dean Dr.A.EDWIN JOE,M.D.,** for having allowed me to conduct this study in our hospital.

I express my heartfelt thanks and deep gratitude to the Head of the Department of Medicine Prof. **Dr. KUMAR NATARAJAN, M.D.** for his generous help and guidance in the course of the study.

I am extremely grateful to **Dr.T.RAVISHANKAR.,** Head of the department of Gastroenterology,for his valuable help and cooperation and allowing me to use institutional facilities.

I am extremely grateful to **Dr.LALITHA M.D.,** Head of the department of pathology,for her valuable help and cooperation and allowing me to use institutional facilities.

I am extremely grateful to **Dr.N.SUNDARI M.D.,** Head of the department of Radiology,for her valuable help and cooperation and allowing me to use institutional facilities.

I am extremely grateful to **Dr.MANIMEGALAI, M.D**(Bio), HOD, Department of Biochemistry, for her valuable help and cooperation and allowing me to use institutional facilities.

I sincerely thank Asst. Professors- **Dr.P.S.MANSHUR.M.D, Dr.V.UVARAJ MURUGANANDAM, M.D,** for their guidance and kindhelp.

My sincere thanks to all my friends and post-graduate colleagues for their whole hearted support and companionship during my studies.

I thank all my **PATIENTS**, who formed the backbone ofthisstudy without whom this study would not have beenpossible.

Lastly, I am ever grateful to the **ALMIGHTY GOD** for always showering their blessings on me and my family

Dr.K.S.DAKSHINAMOORTHY.

ABBREVIATIONS

NLR	–	NEUTROPHIL TO LYMPHOCYTE RATIO
PMN	-	POLYMORPHONUCLEAR CELLS
HE	–	HEPATIC ENCEPHALOPATHY
TNF	-	TUMOUR NECROSIS FACTOR
IL	–	INTERLEUKINS
USG	–	ULTRASONOGRAM
MELD	–	MODIFIED END STAGE LIVER DISEASE
CTP	–	CHILD TURCOTTE PUGH SCORE
UKELD	-	YNITED KINGDOM MODEL END STAGE LIVER DISEASE
UGI	–	UPPER GASTROINTESTINAL
MCL	–	MID CLAVICULAR LINE
C3	-	COMPLEMENT FACTOR 3
NK CELL	–	NATURAL KILLER CELL
GIT	-	GASTROINTESTINAL TRACT
NAFLD	–	NON ALCOHOLIC FATTY LIVER DISEASE
CLD	–	CHRONIC LIVER DISEASE
DIC	–	DISSEMINATED INTRAVASCULAR COAGULATION
KF RING	-	KAYSER FIEISCHER RING

AST – ASPARTATE TRANSAMINASE

ALT – ALANINE TRANSAMINASE,

ALP - ALKALINE PHOSPHATSE

GGT - GAMMA GLUTAMYL TRANSFERASE

INTRODUCTION

Liver is one of most important and fascinating organ of the human body. Human liver performs a lot of diverse functions, its functional heterogenicity is unmatchable and fascinating, and it is rightly known as the metabolic factory of the body. So on this background liver disease becomes a highly important area of concern for humans and it is one of the highly taxing disease to have of a person both physically, mentally and financially. Liver disease can be acute or chronic. Various causes of liver disease carry variable degree of mortality and morbidity. Chronic liver disease can occur because of variety of reasons. Generally south east Asia which includes our country is ,more prone for viral hepatitis ,and moreover alcoholism is becoming more and more prevalent in our country and our people are more prone to develop cirrhosis with comparatively lesser amount of alcohol intake and lesser duration when compared to the western population. This makes chronic liver disease of alcoholic cause more prevalent in our country. Next the new pandemic that is becoming more and more common is fatty liver, that is now identified as a part of metabolic syndrome, is leading to NASH , and finally to cirrhosis. Because of the above said reasons and also accounting for some of the rarer causes of liver disease , chronic liver disease and its complications have become more common in India. In chronic liver disease when the patient is in a compensated state, his lifespan, mortality rate productivity etc. very good when compared to a decompensated state, when the chances of complications and mortality are very high. So if we can identify the particular group of patients who are more prone to get decompensated and prevent it, we can reduce the mortality and morbidity associated with decompensation. A tool

that is simple, easily available, reproducible and more importantly cheap is the need of the hour. And one such tool, is the neutrophil to lymphocyte ratio. Neutrophil to lymphocyte ratio is one of the newly developed novel marker of inflammation, that can be used as a marker in stable cirrhosis patients to predict the occurrence of decompensation.

AIM AND OBJECTIVES

AIM:

Neutrophil-to-lymphocyte ratio (NLR) is a novel inflammation index that has been shown to independently predict poor clinical outcomes.

The aim of the study is to evaluate the role of NLR as a prognostic marker in patients with stable liver cirrhosis

OBJECTIVES:

To identify early, the group of stable cirrhotic patients with likelihood of developing complications in the near future.

REVIEW OF LITERATURE

Cirrhosis of liver is one of the major contributors of morbidity and mortality in India. Liver cirrhosis accounts for 2.44 % of total deaths in India.

Unlike in the past when liver cirrhosis was thought irreversible, now in certain conditions like chronic hepatitis C, hemochromatosis and alcoholism, it is proved that reversal of cirrhosis is possible.

This makes the early prediction of complications in a liver cirrhosis patients all the more important, so that early intervention can be made ,thus preventing the progression of patients from a compensated to decompensated state and so increasing the chances of survival, and in certain conditions , reversal of cirrhosis depending upon the causative factor.

One of the tools to predict early, the development of complications in liver cirrhosis patients is Blood Neutrophil to Lymphocyte ratio.

Neutrophil to Lymphocyte Marker is a simple bedside marker of systemic Inflammation. It has been used in a lot of studies in different fields of medicine.

Murat biyik et al in his study of Blood neutrophil to lymphocyte ratio independently predicts survival in patients with liver cirrhosis has used NLR ratio as a tool for predicting the survival of patients in his study. The study showed that NLR is an early predictor of mortality in liver cirrhosis patients independent of CTP and MELD scores.

NLR ratio is used as a prognostic factor in solid tumours in a study conducted by Arnoud J. Templeton et al.

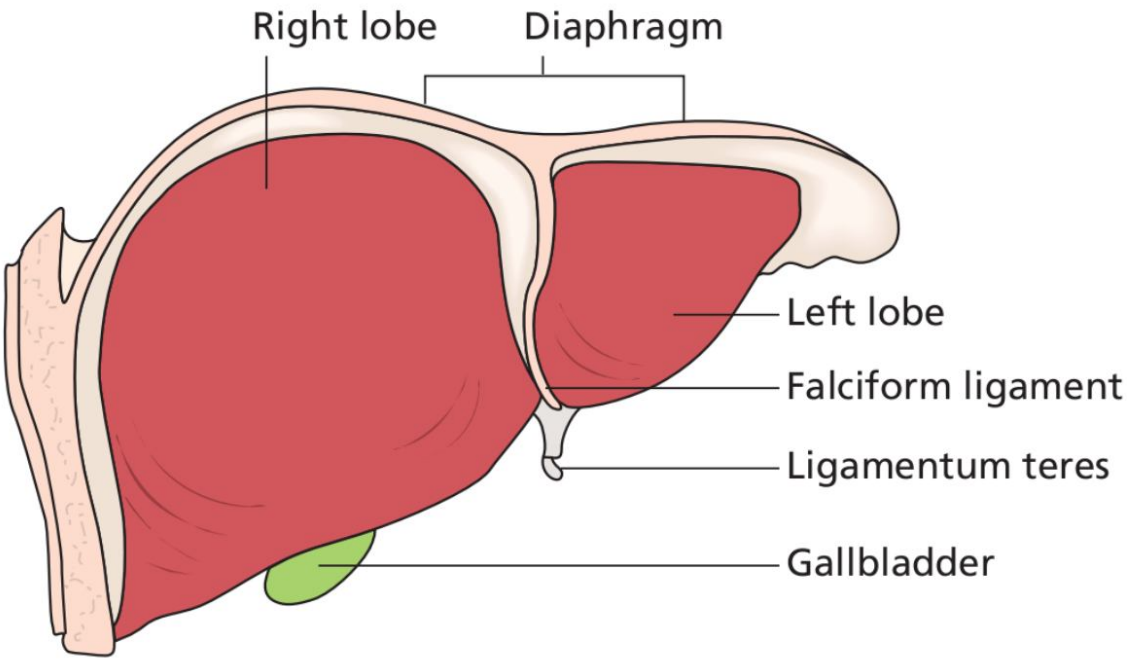
NLR ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population is done by FauziaImtiaz et al. which concluded that systemic inflammation measured by NLR has a significant association with chronic conditions prevalent in the general population.

All the above studies signify the importance and relevance of neutrophil to lymphocyte ratio as a tool to diagnose systemic inflammation.

ANATOMY OF LIVER

Liver is the biggest solid organ of the body with an approximate weight of 1800mg in men and 1400mg in women, and extends from 5^{th}intercostal spaceto the right costal margin in the mid-clavicular line.

Liver has 2 lobes, the right lobe and left lobe, it is being divided in the anterior aspect by the falciform ligament, in the posterior segment by the ligamentum venosum and inferior segment by the fissure for the ligamentum teres. The quadrate and caudatlobe are also part of the right lobe of liver



.

FIGURE 1: ANATOMY OF LIVER

The Hepatic artery which is a branch of the coeliac axis supplies the liver. The portal vein drains blood from the intestine and spleen drains into the liver. Liver is entered by these vessels through the inferior surface through the porta-hepatis. The right bile duct and left bile duct drain bile from the corresponding lobes and join together as the common hepatic duct, and the cystic duct which arises from gall bladder joins the common hepatic duct and give rise to the common bile duct which opens into the 2nd duodenum in its second part.

Each Hepatic lobe is made up of many hepatic lobules, which are the structural and functional units of the liver. The hepatic lobules are made-up of hepatocytes. Surrounding each of the hepatic lobule is the portal triad.

The portal triad consists of a

.Branch of hepatic artery

.Portal vein

.Tributary of bile duct.

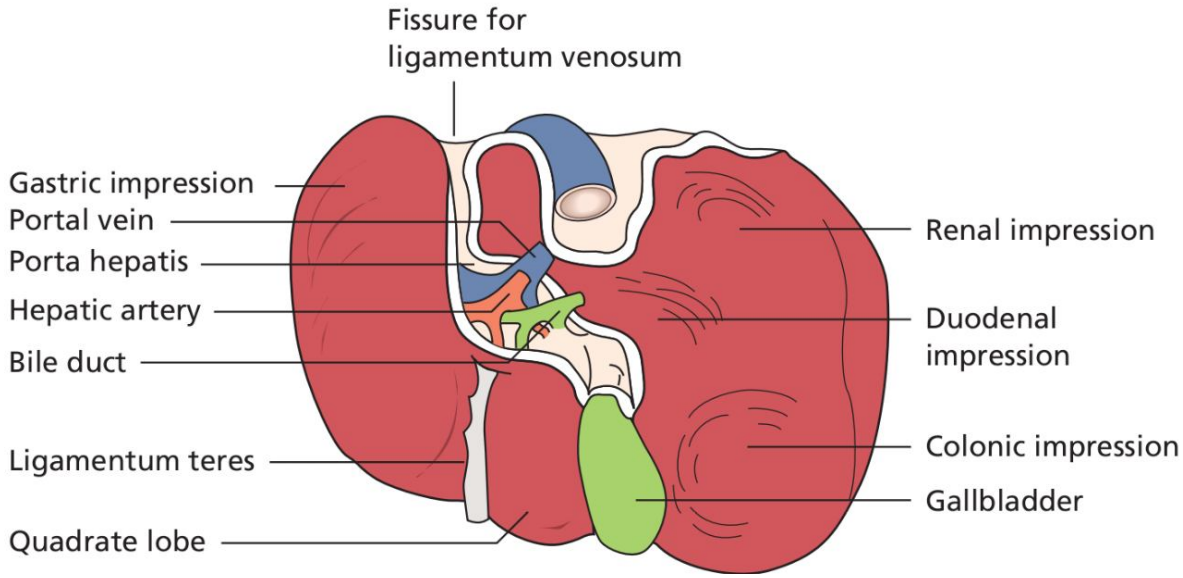


FIGURE 2 - INFERIOR SURFACE OF LIVER

According to the Couinaud classification liver [1] is divided into 8 segments.

The centre of the segment has the branches of the portal vein, hepatic artery and bile ducts, and the hepatic veins lie in the periphery.

The 8 segments are the superior anterior, superior posterior, inferior anterior and the inferior posterior segments of the Right lobe and superior lateral and superiormedial , inferior-medial and inferior lateral segments of the left lobe.

The caudate lies separately in the posterior part of the liver. Surgical dissection along the planes between these segments is relatively bloodless.

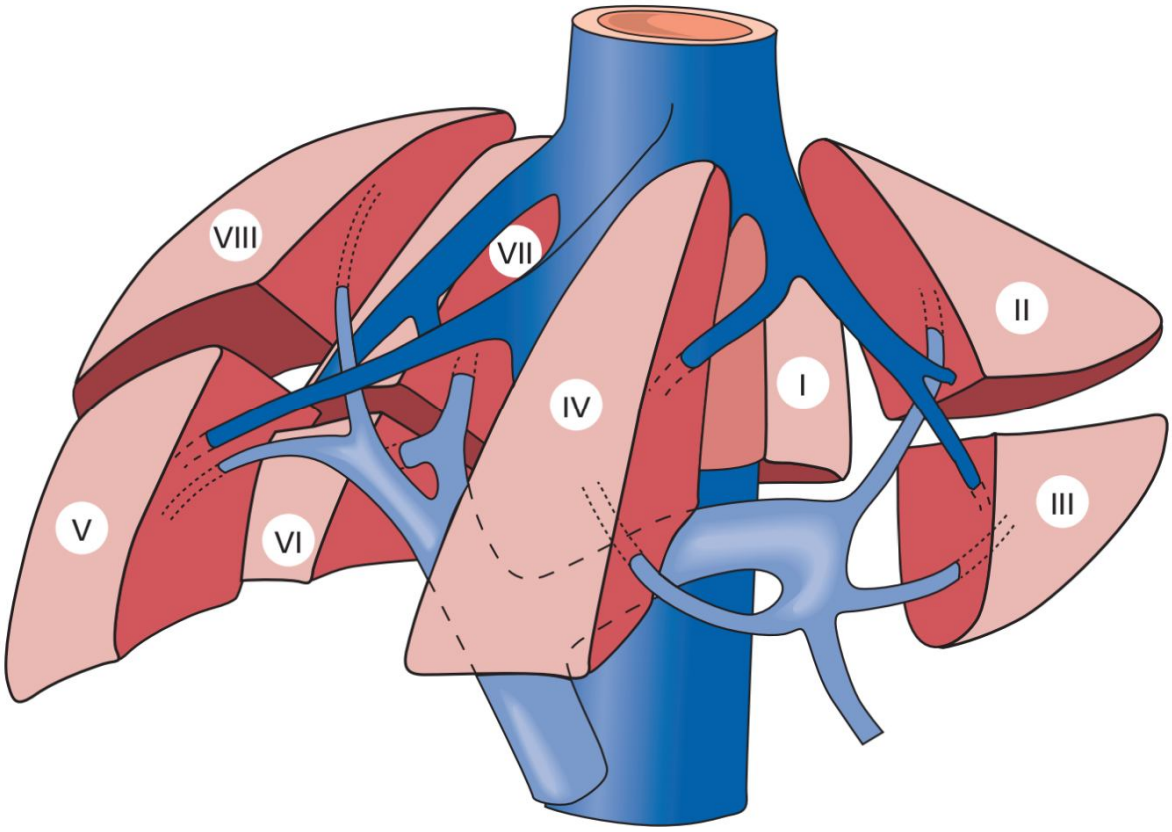


FIGURE 3 - SEGMENTAL ANATOMY OF LIVER

Liver and its surface marking in the body:

Upper border of right lobe - 5th rib 2cm medial to MCL.

Upper border of left lobe - upper border of sixth rib.

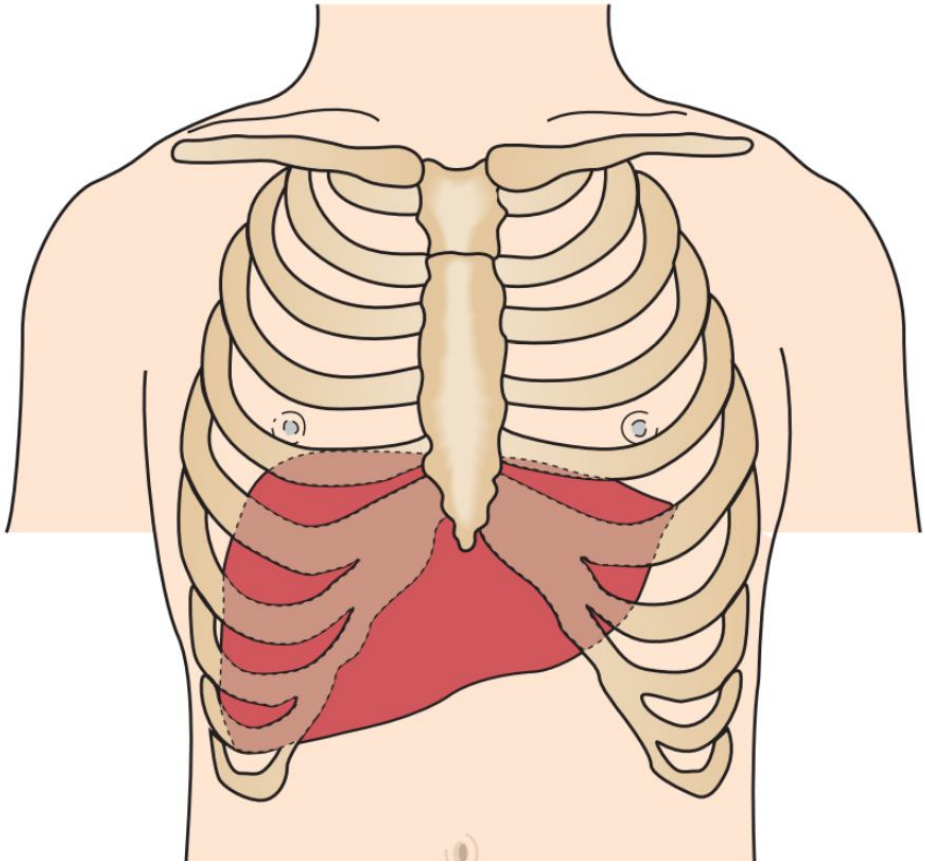


FIGURE 4 – SURFACE MARKING OF LIVER.

Lower border – oblique line from right ninth rib to left eighth rib.

Microanatomy of liver:

Human liver consists of cords of liver cells[3].They radiate from a central vein and the sinusoids are found in between them. the portal veins drain into the hepatic

sinusoids. Blood usually flows from the portal vein to the hepatic sinusoids, but it get altered when there is portal hypertension.

The portal triad[4] consists of three components that includes a bile ductule, portal vein radicle and a hepatic arteriole[3]. Portal tract is surround on all directions by the hepatocytes.

The hepatocytes comprise the major part of the liver forming around 60% of the total liver. it doesn't have a basement membrane and usually has got a lifespan around 150 days.

The hepatic sinusoids[6]is lined by the endothelial cells and the kupfer cells are found on the hepatic sinusoids in the vascular aspect.

Space of disse[7] is a space between the sinusoidal endothelium and the hepatocytes. The hepatic stellate cells and few collagen fibrils are found in the space of disse.

The stellate cells[8] store fat lobules and so are also termed as lipocytes. They also store vitamin A. on activation the stellate cells get transformed into myofibroblasts. The myofibroblasts synthesize collagen. The lymphatics are found in the connective tissue surrounding the portal triad.

Bile canaliculi[9] form the basic unit of excretory system of liver. The canals of hering into which the biliary canaliculi from the lobes drain, connects the short bile ductules and the terminal bile ducts.

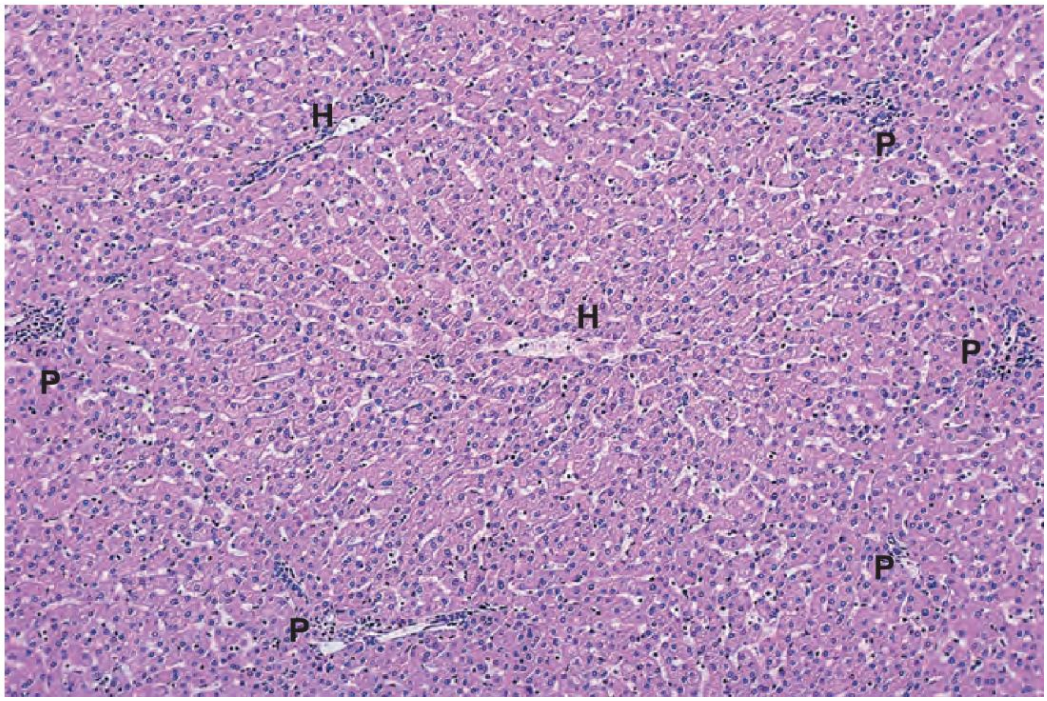


FIGURE 5 – MICROANATOMY OF LIVER

Liver functional heterogenicity:

Structural/functional properties of hepatocytes vary according to acinar[5]locations.for example the zone 3 contains the p450 enzymes which are involved in drug metabolism. So the zone 3[10,11] receives receives the maximum amount any toxin that enters the liver, and so they are prone for adverse drug reactions like centrilobular necrosis.

Death and regeneration of liver cells:

Necrosis and apoptosis are the two mechanisms[12,13] by which liver cell death occurs. In necrosis there is nonviable organelles, loss of plasma membrane ,pyknotic chromatin ,ischaemia and inflammation.

Apoptosis[14] is characterised by viable organelles, fragmented DNA, apaoptotic bodies and absence of inflammation..

During regeneration circumstances, the cytokines[15] stimulate the quiescent cells into primed state and then the growth factors cause synthesis of DNA and replication of cells. In a state of impaired response hepatocytes can be obtained from the stem cells in the canal of hering.

Neutrophil to Lymphocyte ratio:

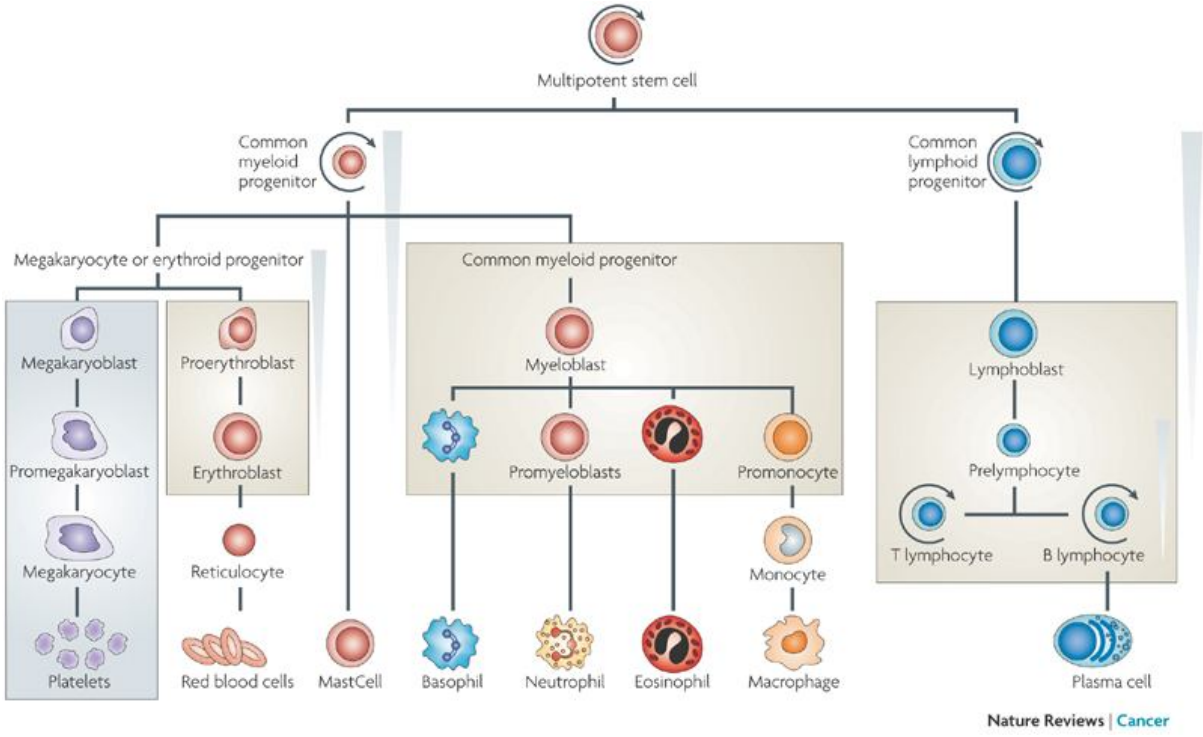


FIGURE 6 – FORMATION OF BLOOD COMPONENT CELL FORMATION

Neutrophils:

Neutrophils are one of the many types of the granulocyte type of cells. They are the most predominant type of the granulocytes. They perform the most integral form of the innate immunity.

They are formed in the pluripotent stem cells of the bonemarrow. When an inflammation occurs, they are usually the first cells to get activated. They are stimulated by many acute phase cytokines and chemokines, like IL-8, LEUKOTRIENE B4 etc. They are the majority of the cells in purulent secretions.

Characteristic features:

Diameter – 12-15 micrometers

Nucleated cells, lobed nucleus, absent nucleolus and rough endoplasmic reticulum.

Neutrophils of femaleshave an extra X chromosome called the neutrophil drumstick.

Usually neutrophils have 3-5 segments, and hypersegmentation is a seen in pathological conditions like vitamin B12 deficiency.

Normal count of neutrophils is 2.5 to 7.5 x 10(9)/L. they form pseudopod like structures when attacking the antigens.

Normal life span of neutrophil without activation is 5 to 90 hours, and if activated 1 or 2 days.

Neutrophils undergo chemotaxis by which they go to the site of infection.IL-8, INTERFERON GAMMA, C3. C5a are all involved in these processes.

- Mechanism of action: They act by 3 major pathways,

Phagocytosis: Neutrophils acts by phagocytosing the microbes, which requires opsonisation. After phagocytosis, they secrete reactive oxygen species and hydrolytic enzymes, which kill the bacteria. Respiratory burst is the term used to indicate the consumption of oxygen during the process.

- Degranulation: Neutrophils release primarily three types of granules,
- Azurophilc granules – cathepsin G, elastase,myeloperoxidases.
- Specific granules – Alkaline phosphatase,etc
- Tertiary granules –Cathepsin, gelatinase.
- Neutrophil extracellular traps: this is a mechanism in which neutrophils form fibers in the form of a web formed by chromatin and serine protease. They play an important role in sepsis as they form a physical barrier and kill the extracellular microbes. NET is also seen involved in pre-eclmapsia.

Lymphocytes:

They are a type of WBC'S. NK cells, B and T cells, are all types of lymphocytes.

T cells are thymus cells that are part of cell mediated immunity, and B or Bone marrow cells are the integral part of the humoral immunity. The main function is to identify the antigens other than the self during Antigen presentation. B cells act by releasing antibodies, and T cells have two types of cells, the T helper cells produce cytokines that induce an immune response, cytotoxic T cellskillby producing toxic

granules. Once activated a fraction of cells become memory cells that last for entire life.

NK cells mainly act in defending the body from tumours and viral infections, by identifying the MHC on the surface of these cells. The special characteristic of it is it doesn’t need to be activated priorly in order to kill other cells,

Lymphocytes have a large nucleus with very little cytoplasm, and the nuclear size is approximately equal to that of an erythrocyte. They have polyribosomes. B and T cells cannot be differentiated by peripheral smear study and can be done only by flowcytometry.

Neutrophil-lymphocyte ratio is defined as the ratio between absolute count of neutrophils and the absolute count of the lymphocytes. It is one of the most simple and fast tools available to measure the systemic inflammation in our body. It is one of the most cost effective, less complicated procedure wise and easily reproducible, doesn’t need skilled labour to perform.

A high NLR ratio occurs when there is a neutrophilia and an associated lymphopaenia, conversely a low NLR ratio occurs when there is a lymphocytosis with an associated neutropenia. High NLR ratio indicates a subgroup of patients who will benefit from therapy with anti inflammatory agents.

The prognostic role of NLR has been implicated in a number of conditions,. In general a high NLR ratio is associated with poorer overall survival and disease free period in lot of disease conditions among which, malignancies of GIT, Gynaecological and CVS , to name a few.

Inflammation has a major impact on the background pathology of number of non-inflammatory conditions, including lot of malignancies and atherosclerosis.

There are a lot of inflammatory markers available, but neutrophil-lymphocyte ratio is more significant compared to others , especially in malignant diseases and cardiac abnormalities.

Neutrophil-lymphocyte ratio shows the balance that exists in-between the body's adaptive immunity and innate immunity and so indirectly between lymphocytes and neutrophils.

Number of research have found out that conditions with elevated levels of cytokines that have proinflammatory properties have been associated with high levels of neutrophil-lymphocyte ratio. This may finally lead to damage of deoxy ribonucleic acid of the cells of the body.

The normal value of Neutrophil-lymphocyte ratio varies according to race and ethnicity.

Neutrophil to lymphocyte ratio is one of the latest inflammatory markers that has numerous clinical implications. The elevated neutrophil count implies active inflammation and the reduced lymphocyte count implies malnutrition and also inflammation. If it is raised it implies poor clinical outcomes. It is cheap, widely available and easily reproducible in all settings.

NLR is obtained by dividing the calculated number of neutrophils by that of lymphocytes.

It has implications in other aspects of medicine like in cardiology and various malignancies especially oesophageal and pancreatic cancer.

Cirrhosis of liver:

Cirrhosis is a process in which the liver undergoes diffuse fibrosis and the architecture of liver gets converted into nodules that are abnormal and it is almost always associated with necrosis of the hepatocytes.

In conditions like schistosomiasis and non-cirrhotic portal fibrosis there is only fibrosis without nodularity and in conditions like nodular regenerative hyperplasia there is only nodularity without fibrosis. In congenital hepatic fibrosis lobar architecture is maintained inspite of fibrosis and nodularity. These conditions doesn't constitute cirrhosis. The portal tract is supplied by branch of hepatic artery.

Classification:

Micro-nodular – nodules less than 3mm in diameter, it is the early stage in which liver is usually enlarged or of the normal size.

Macro-nodular – Nodules more than 3mm in diameter and the liver is usually shrunken

Mixed - equal presence of both micro and macro-nodular components

Causes:

In our country the most common cause for cirrhosis is alcohol. It constitutes around 50% of the cases. The next common aetiology being hepatitis B infection. It constitutes around 30-70% of the cases. Following hepatitis B is hepatitis C infection. There is a subset of persons who have both alcohol abuse and also infected with hepatitis B/C[1] and the proportional contribution of either of these causes is highly variable.

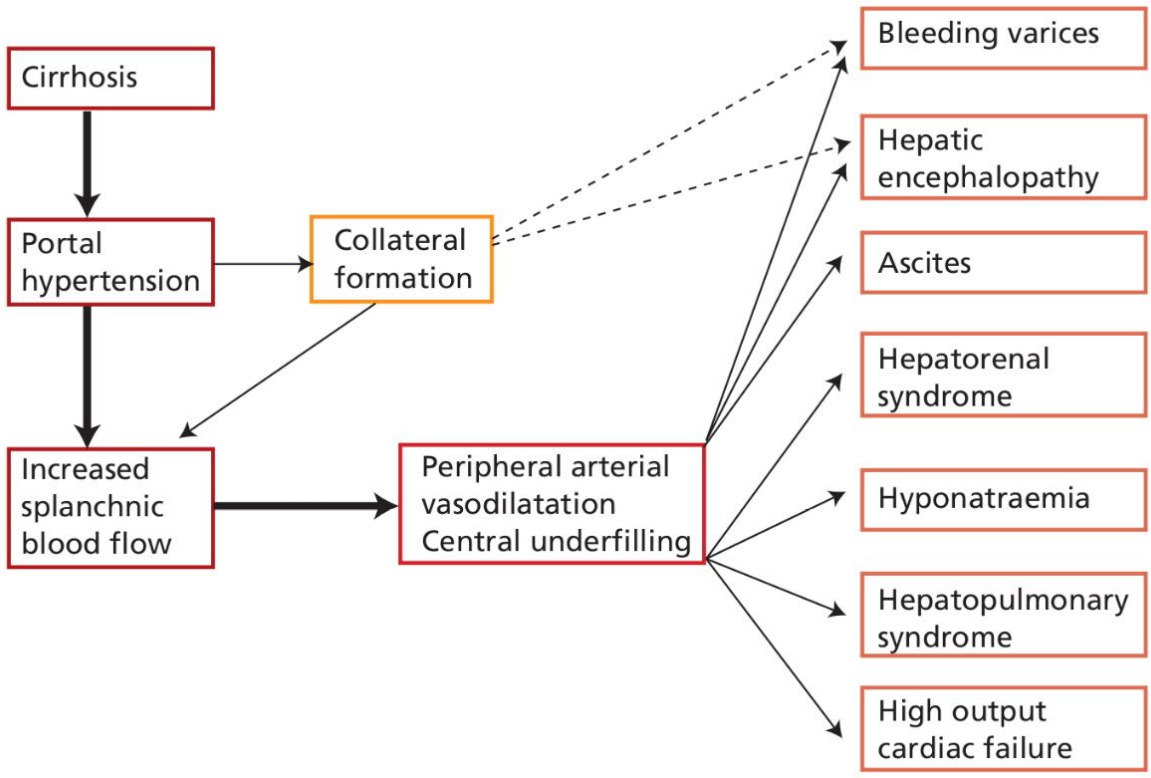


FIGURE 7- CLINICAL SPECTRUM OF CIRRHOSIS

The Indian population of people are more prone to fibrosis when compared to the western populations and they develop cirrhosis with relatively lesser amount and lesser duration of alcohol intake. The main reasons being the poor nutrition, and lesser build along with high usage of country liquor. Another important cause is the high prevalence of concurrent Hepatitis infection.

Mycotoxins and Malnutrition are factors that initiate or aggravate a pre-existing cirrhotic process but usually don't cause cirrhosis independently. Non alcoholic Fatty liver disease {NAFLD} is another important cause of liver cirrhosis in recent times.

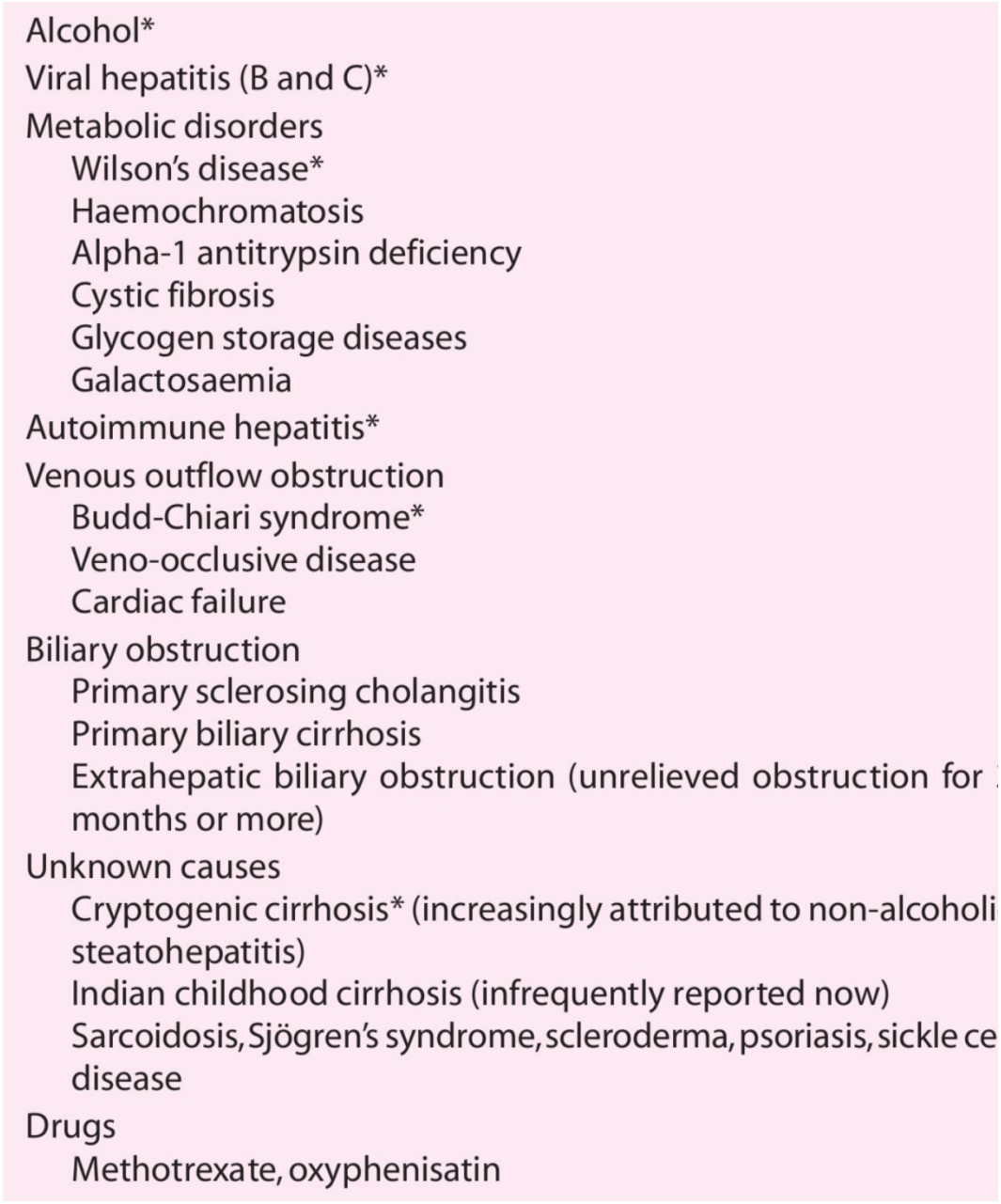


FIGURE 8 – CAUSES OF LIVER CIRRHOSIS

Pathogenesis:

There are 3 major mechanisms of cirrhosis

Hepatitis:

In many instances, particularly in viral hepatitis, there will be necrosis of the lobular hepatocytes and central portal bridges and there will also be piecemeal necrosis of the hepatocytes.

Fatty Liver:

Leading route of cirrhosis in alcoholics. There will be ballooning of the hepatocytes which contains macro-vesicular fat deposits and Mallory bodies. They will be surrounded by inflammatory cells like neutrophils and lymphocytes and collagen.

Portal and centri-lobular fibrosis :

In patients with bile duct disorders and venous outflow obstruction, there will be cirrhosis due to fibrosis in the portal tracts.

Above said processes lead to fibrosis and distortion of liver architecture. Along with this there can be a concurrent regeneration process. All these necrotic changes leads to porto-systemic shunting of blood inside the liver.

There will be deposition of collage in the space of disse and also the regenerative nodules compressing the vasculature that ultimately results in portal hypertension.

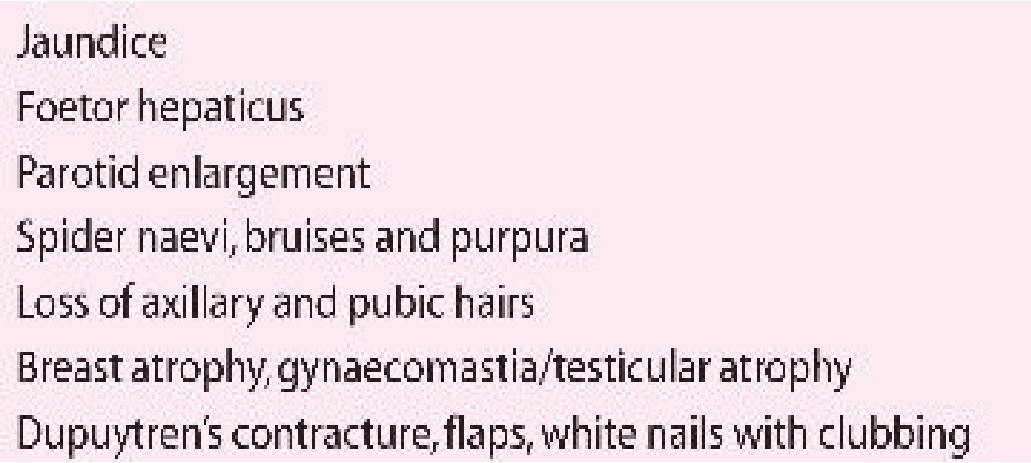
Clinical features:

Liver is an organ with unique regenerating capacity. Just 10%of the total liver cell mass is enough for maintaining the metabolic functions of the liver. Because of these features, around 30% of the cirrhotic patients are asymptomatic.

Initial manifestations of liver cirrhosis includes easy fatiguability and generalized weakness. There will be associated muscle wasting especially prominent in the upper limb muscles and ususally not evident in the lower limb because of the associated edema. Patient will experience weight loss which is not eveident initially because of the retention of fluids.

There are certain physical signs that indicate hepatocellular failure in a patient, the major features are listed below.

FIGURE 9 – CLINICAL FEATURES OF CIRRHOSIS



Spider naevi[17]is a sign that is commonly seen in chest upperlimbs and sometimes in the face also. Spider naevi consists of a central arteriole with capillaries radiating from the centre. There will be obliteration of the spider naevi once external

pressure is applied over that. The size is usually a few milimeters, but rarely sometimes it can be larger in size and cause bleeding from the site of the naevus.

Other common conditions associated with spider naevi are pregnancy and rheumatoid arthritis and also in patients on hormonal therapy such as estrogens.

FIGURE 10 - SPIDER NAEVI

Sometimes they can be found in normal persons. Palmar erythema [19]is a clinical condition in which there will be reddening of the thenar and hypothenar regions of the palms. Fingertips may also be involved. Rest of the palms are usually not involved

FIGURE 11 – PALMAR ERYTHEMA.

Gynaecomastia[20] is one of the presentations. it occurs because of two possible mechanisms,[21]. .One is because of the conversion of the androgens to estrogens in the peripheral tissues, another cause is usually related to the usage of the drug spironolactone in the treatment of liver cirrhosis.

FIGURE 12 - GYNAECOMASTIA

Hypogonadism manifests in both males and females equally. In men it usually causes loss of libido and atrophy of the testicles, more commonly in alcoholics than others. In women the common manifestation is menstrual abnormalities[22,23] in the form of oligomenorrhoea and amennorhoea.

Infertility can occur in both males and females.

Anaemia occurring in cirrhosis patients and the cause are multifactorial. That includes iron folate deficiency , bone marrow hypofunction and blood loss because of UGI bleeding, hemolysis especially in the extravascular component and a hyperfunctioning spleen.

There will be associated coagulation abnormalities found. It is mainly because of abnormalities in the synthetic function of the liver, leading to reduced synthesis of the clotting factors. The other factors contributing to the coagulation impairment are thrombocytopenia caused by hypersplenism and DIC.

Ammonia smell of the breath commomly known as foetor-hepatis[24]can occur . white opaque nails called Leuconycia is also one of the manifestations.

Duputryens contracture which occurs predominantly in the alcoholics is a hand deformity that occurs over a period of years, due to thickening and contracture of the palmar fascia.

Clubbing of all the digits is found in some of the patients.

Patients may have an underlying low grade pyrexia.

Wilsons disease should be ruled out in case of young cirrhosis patients by looking for the presence of KF ring under slit lamp.

The other features of decompensation in cirrhosis include, jaundice, ascites, pleural effusion[hydrothorax], Gastrointestinal bleeding due to portal hypertension, and hepatic encephalopathy. Severe jaundice shows downhill prognosis.

Ascites occurs because of portal hypertension which cause high high hydroststic pressure and low albumin causing low osmotic pressure. Ascites is frequently associated with pedal edema, abdominal distension and loss of appetite. Infrequently it is associated with umbilical or inguinal hernia.

Examination usually reveals a dilated abdomen with fullness of the flanks. A thin abdominal wall is present due to loss of muscle mass and subcutaneous fat. Dilated veins are also found frequently.

Caput medusa is a condition in which dilated veins are found radiating outwards from the umbilicus and it indicates portal hypertension.

Puddle sign helps to diagnose very small amount of fluids but it has got few disadvantages like inconvienience for the patient and unreliable nature of the test.

Shifting dullness and flank dullness indicate a minimum of 1500ml of fluid in the peritoneal cavity.

Fluid thrill is a sign that can be elicited when there is tense ascites, in this condition fluid thrill will be usually could not be elicited, and organomegaly could not be made out inspite of deep palpation.

A few patients develop right sided pleural effusion due to seepage fluid into the pleural cavity by negative intrathoracic pressure through the diaphragmatic defects.

Upper gastrointestinal bleeding is a frequent feature of hepatic cirrhosis due to portal hypertension. When there is an increased portal hypertension, decompression occurs via bleeding from the esophageal varices. Gastric fundal varices may also bleed sometimes. Ectopic varices may be found in other parts of the gastrointestinal tract but they don't bled usually gastric erosions, peptic ulcers and congestive portal gastropathy may also lead to bleeding in these patients.

Anatomical abnormalities of liver:

Accessory lobes:

Rarely accessory lobes can occur in human beings, and it is usually without any clinical insignificance. It is incidentally found out during routine scanning. It is usually found in the inferior surface of the liver and has got its own blood supply and bile duct. Sometimes they may require surgical removal because of twisting around their own axis.[8,9]

Riedal's lobe:

It is a normal anatomical variant. Downward projection of the right lobe and it is usually tongue shaped[25] and common in females compared to males. It is a mobile tumour that may wander from the diaphragm to the right iliac region. It usually don't cause any symptoms, but sometimes it may be a site of hepatic metastasis or primary hepatocellular carcinoma. Close differential diagnosis includes visceroptic tumours of the right kidney.

Corset liver

It occurs because of an unknown mechanisms in elderly women wearing corsets[26] for long duration. It occur as horizontal furrows on both lobes of the liver.

Lobar atrophy:

It usually occurs because of obstruction of the portal supply or biliary drainage. Atrophy of Left lobe is more common. The affected lobe is shrunken and fibrosed. The opposite lobe undergoes compensatory hypertrophy. Benign biliary stricture[27]or

cholangiocarcinoma are the frequent reasons found with lobar atrophy. In these conditions ALP levels are usually elevated.

Agenenis[28] of right lobe:

It is one of the causes of presinusoidal portal hypertension. It should be differentiated from other conditions causing lobar atrophy. Compensatory hypertrophy of the left lobe of the liver occurs.

Situs inversus:

It is a very rare congenital anomaly. There are two subtypes, situs inversus totalis and abdominal is. In both these conditions liver is found in the left hypochondrium. Other common anomalies found in these syndromes includr aberrant hepatic artery syndrome , congenital absence of portal vein, poly-spleenia and atresia of the biliary tree. Surgical treatment may be an option in the above disorders.

Liver function tests:

Liver function cannot be assessed by a solitary test, but only by a combination tests. These test indicate not only the functions of the liver but also the patterns of the liver injury.

There are three patterns of LFT abnormalities.

Hepatocellular pattern – AST and ALT elevations

Cholestatic pattern – ALP and GGT elevations

Infiltrative pattern –ALP,GGT AND BILIRUBIN elevations.

Jaundice evaluation:

The important components are ALP,AST/ALT, and bilirubin levels.

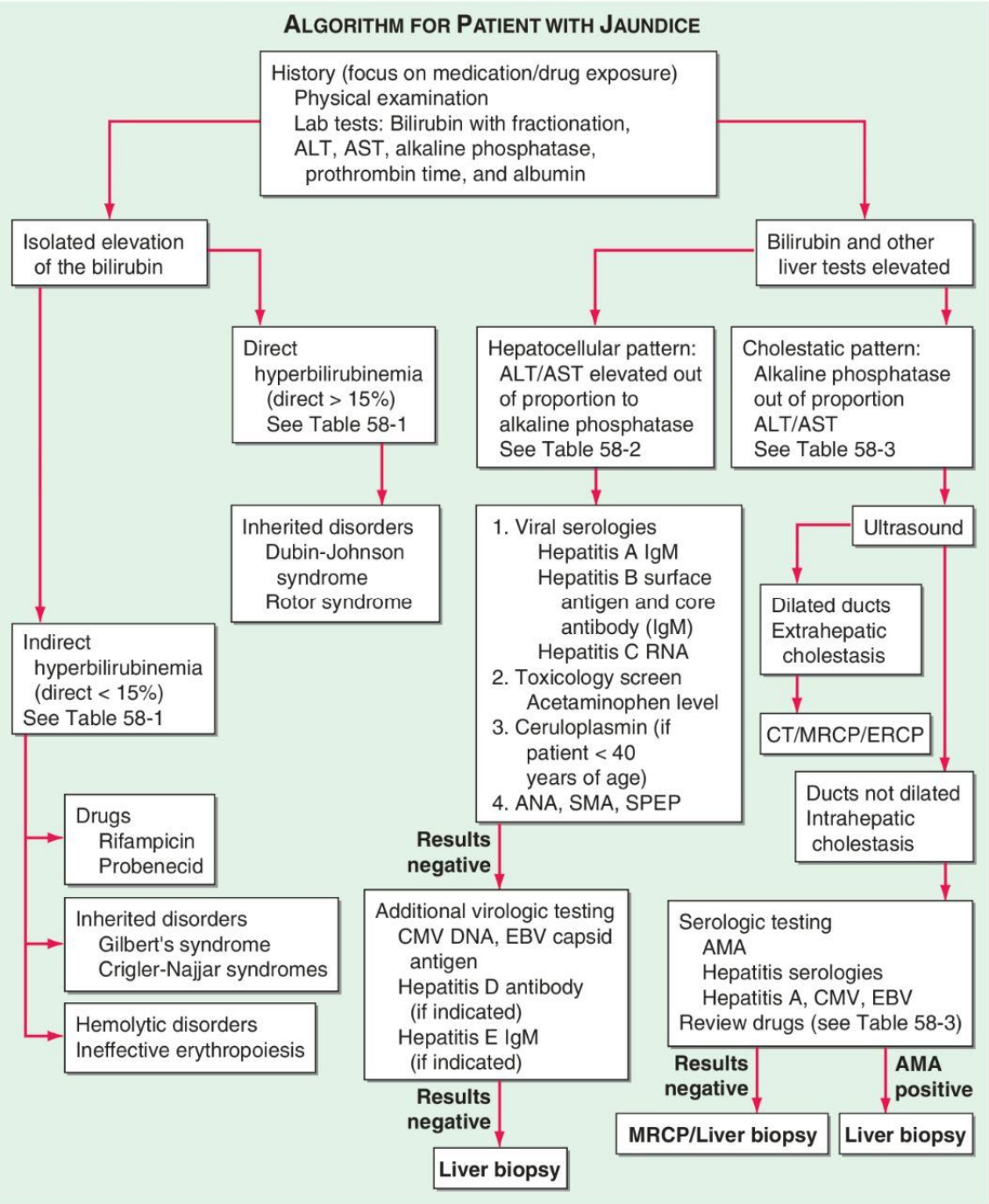


FIGURE 13 – APPROACH TO A CASE OF JAUNDICE

Assessment of liver cell damage:

Serial values of Total bilirubin, albumin post vitamin K prothrombin time, Arterial ammonia levels especially in acute liver injury.

TABLE 1 - LIVER FUNCTION TEST

NAME OF THE TEST	DIAGNOSTIC UTILITY
Total bilirubin	To calculate the severity of jaundice
Conjugated bilirubin	Any cause of haemolysis, Gilbert syndrome
Alanine transaminase	Alcoholic liver disease
Aspartate transaminase	Hepatocellular disease pattern diagnosis
Gamma Glutamyl transferase	Biliary cholestasis and abuse of alcohol
Alkaline phosphatase	Infiltration of liver, cholestasis.
Albumin / prothrombin time	Synthetic function of liver

BILIRUBIN:

VAN DEN BERGH DIAZO REACTION is used for identifying the levels of the serum bilirubin. Sulphanilicacid[29] is added to plasma and the diazonium ion reacts with bilirubin and produces azo derivatives which are detected by spectrophotometric methods. This test calculates the total and indirect fractions of bilirubin from which we can determine the value of direct bilirubin. The only disadvantage of this method is that it can be sometimes inaccurate especially in low

values. Other methods include alkaline methanolysis , determination by spectrophotometry[30], HP-Gas liquid chromatography.

Clay coloured stools occur in cholestatic, normal colour in haemolytic jaundice and pale in bilirubin glucuronyl transferase defieciency.

Bilirubin doesn't appear in urine in normal circumstances, because unconjugated bilirubin that is present in serum is insoluble as it is attached to albumin. Bilirubin glucoronides which are products of bilirubin metabolism appear in urine.

Enzyme tests analysis:

These test shows the type of injury of liver but don't help in differentiating between the exact causes. They guide us on further evaluation of the condition.

Aminotransferases:

Aspartate amino transferase: Usually found in the mitochondria and cytoplasm. It is predominantly present in liver , followed by heart and skeletal muscles. It is also found in kidneys, brain, lungs, leucocytes pancreas and erythrocytes. AST is markedly reduced in long term haemodialysis.

Alanine aminotransferase: Usually found in the hepatocyte cytoplasm. More specific than AST.

VIRAL HEPATITIS conditions show elevated AST and ALT. They don't indicate the severity of liver damage. They have short half –lives[31]. Even with falling enzyme levels patient may have acute necrosis of the liver.

Conditions like NAFLD[34], alcohol abuse[33], haemochromatosis, and less commonly wilsons disease, anorexia nervosa can cause elevation of enzymes.

Conditions causing massive elevations of enzymes are viral hepatitis, acetaminophen toxicity, ischaemic hepatitis and hepatitis due to autoimmune[32] conditions. Cholangitis also cause high values.

AST/ALT ratio more than 2 shows acute liver disorder, NAFLD and chronic hepatitis C.

ALKALINE PHOSPHATASE: It is a an enzyme found in the cytosol of hepatocytes. It is also found in membranes ofsinusoids and canaliculi. It rises predominantly in cholestasis when compared to liver injury. It is predominantly found in placenta, ileal mucosa kidney bone[35] and liver, but the major contributors for the serum ALP is liver and bone. Levels are initially normal because it has to be synthesised newly. physiological rise is seen in O and B blood group patients because they secrete ALP from intestine postprandially. Elevation also occurs in sepsis, hepatic tumours, hepatic infiltrations, and haematological disorders involving the liver.

Low levels are found in hypothyroidism, Wilson's disease etc.

GAMMA GLUTAMYL TRANSPEPTIDASE:

GGT is found in epithelial membranes of bile ducts and levels are increased in cholestatic conditions and diseases of hepatocellular conditions. Alcohol abuse can lead to isolated rise of GGT levels. Other conditions with elevated GGT are hepatobiliary disorders, COPD, hyperthyroidism, connective tissue diorders like

rheumatoid arthritis, and several drugs like carbamazepine, furosemide, sodium valproate, phenytoin etc. It has got a high sensitivity for intrahepatic cholestatsis.

Lactate dehydrogenase:

It has got 5 isoenzymes, and it ispredominant in the cytoplasm of liver cells. Elevated in both primary and metastatic liver malignancies, and ischaemic hepatitis. The ALT/LDH ratio is highly elevated [>1.5] in viral hepatitis,when comparedto toxic and ischaemic hepatitis[37].[<1.5].

Quantitative liver function:

Albumin levels and prothrombin time gives an idea about the synthetic ability in liver. But the synthetic function is sustained until very last stage of the disease. Serial assessment of the values is helpful in monitoring of the progression of the disease. They don't play a major role on the part of diagnosis of the disorders.

Liver and Lipids:

Cholesterol though produced in all parts of the body, the most important part is liver. HMG-COA REDUCTASE, is an enzyme. It catalyses the most important rate limiting reaction of cholesterol synthesis is found exclusively in the periportal cells.

Liver also plays an central role in metabolism of lipoproteins. VLDL, which acts as a carrier of both triglycerides and cholesterol is produced in the liver. As it enters the peripheral circulation , the triglycerides are metabolized by lipoprotein lipase, which converts VLDL into IDL and then eventually to LDL which is the most important carrier of cholesterol in our body. HDL helps in the removal of cholesterol

from the peripheral tissues of our body and it is either taken up by liver or get converted to LDL. In cholestasis there is an increase in cholesterol levels due to many mechanisms including increased synthesis by the liver.

Hepatic fibrogenesis:

Fibrogenesis occurs as a response to liver injury that is chronic. Stellate cells play a very important role in the process. Normally there is a basement membrane between the sinusoidal lumen and space of disse. Kupfer cells are found in the sinusoidal side and endothelial cells are found in the other side. Usually all the nutrients pass through the base of the hepatocyte through the sinusoidal fenestrae. This routine is disturbed in fibrosis and liver injury. Type 4 collagen, glycoproteins are the components of the normal basement membrane. After an insult occurs there is a large increase in extracellular matrix. Collagen I and iii are the main components.

Stellate cells:

They are the important aspect of this entire fibrogenesis process. These cells store vitamin A normally. They lie in the space of disse. The normal function of the stellate cells is to produce type 4 collagen. In circumstances where there is hepatocyte injury they undergo a process called switch of phenotype. This leads to a lot of phenotypical changes including loss of vitamin A and type 1 collagen synthesis. On activation of hepatic stellate cells it undergoes to processes ie, initiation and perpetuation. On effective management and removal of the initiating event, for example alcohol absitenence, the stellate cells go back to normal quiescent stage or else they are removed.

After the initial event of activation the stellate cells undergo rapid proliferation, with PDGF being the most strong growth factor.

The next process that occurs is the contractile process of stellate cells. This is the reason for the higher pressure in the portal system even during the early part of the process of fibrosis. But this is reversible the main mediators of this are nitrogen oxide and endothelin-1.

Stellate cells play the central role in fibrogenesis. TGF-BETA1 is the strongest cytokine involved. Synthesis of collagen 1 is the most important feature.

Stellate cells move to the area of injury and the resultant fibrosis by chemotaxis. The main chemotactic mediators are, PDGF AND CXCR3.

Inflammatory mediators:

Stellate cells has an important role in inflammation. Cytokines involved in inflammation are secreted by them. They also present antigens like dendritic cells to the major histocompatibility complex 1 and 2. They are also involved in toll like receptor signalling.

In other scenarios various other cells are also involved in inflammation. Biliary fibrosis is mediated portal myofibroblasts.

In the setting of chronic liver disease , circulating cells from the bone marrow may settle down in liver and may mediate hepatic fibrosis.

Clinical features:

Liver biopsy[38] is one of the methods of staging hepatic fibrosis, but the process of liver biopsy itself is complex and carries with it a lot of complications, discomfort to the patients etc. furthermore there is a big chance of sampling errors[39], that is difficult to avoid.

Noninvasive markers for hepatic fibrosis are readily available,which includes both and direct and indirect mediators.examples include AST/ALT, MATRIX METALLOPROTEINASES etc. The estimated prevalence of the disease in the population that is going to be tested is very important in interpreting the results of the non-invasive markers. These markers helps us to differentite between F1 to F4. The disadvantage is that they can't differentiate other intermediate stage clearly.

All the routine imaging systems like USG, CT & MRI can detect cirrhosis only at a later stages when there is development of portal hypertension. Earlier stages of cirrhosis are easily missed.

Fibroscan[40] is one of the latest techniques which measures the liver stiffness offers hope in this aspect ,as it is able to detect cirrhosis at a far earlier stages.

Other latest techniques are CE-enhanced USG, which measures flow of blood with gas filled microbubbles.PET imaging[41] and magnetic resonance spectroscopy are other newer modalities.

Cirrhosis of liver:

It is a process in which is there is diffuse involvement of liver in the form of fibrosis and nodule formation.

Causes of cirrhosis are many and vary in various parts of the world. For example viral hepatitis still remains as the leading cause in the developing countries, in the western world NASH and alcoholism are the leading causes.

Cryptogenic cirrhosis is a condition were no cause could be found as the predisposing factor for cirrhosis.

Multifactorial causation of cirrhosis:

There are conditions in which there are single cause of cirrhosis and others in which there are is a single major cause and multiple other co-factors. For example viral infection[44] and primary biliary cirrhosis have single causative agent. Sometimes associated conditions like alcohol intake in a pre-existing viral hepatitis, old age with any cause of hepatitis , patients with diabetes have faster progression of disease when compared to others with the absence of these co-existing conditions

Diagnosis:

Liver cirrhosis can be diagnosed by presence of fibrosis along with the presence of nodules all over the liver.

FIGURE 14 – MACRO NODULAR CIRRHOSIS

FIGURE 15 – MICRONODULAR CIRRHOSIS

Although liver biopsy is considered as the gold standard for the diagnosis of liver cirrhosis , it has its own limitations in the form of complications , errors of sampling, the size of the sample, contraindications for liver biopsy etc. Even with all of these confounding factors a Good histopathological examination can diagnose the cirrhosis with the help of the background clinical conditions and other relevant investigations.

The diagnosis like alpha-1 antitrypsin deficiency, autoimmune liver disease etc are now increasingly being diagnosed by liver biopsy[42][43], reducing the burden of cryptogenic cirrhosis cases.

Biopsy via trans-jugular liver procedure is one of the ways to obtain liver tissue in patients in whom the conventional approach is contraindicated, like patients with massive ascites and coagulopathy.

USG abdomen is especially useful in diagnosing HCC in the setting of pre-existing cirrhosis, diagnosing the presence of even the small collections of fluid in the peritoneal cavity, and details about the portal vein like its, diameter, patency, direction of blood flow.

Computed tomography of liver is useful in identifying the finer details of the nodules , and also recording the progression of the disease. They are particularly sensitive in identifying the SOL'S of the liver, both primary and metastasis. CE-CT, helps us to diagnose the abnormalities of the portal circulation. CT guided biopsy is particularly useful in the diagnosis of focal lesions. The only disadvantage of CT scan is the concerns about the dose of radiation exposure, particularly in lesser age group when serial imaging is required.

MRI imaging is also useful, but the disadvantage is the cost factor. It is particularly useful in assessing the abnormalities associated with the biliary system. It is also very useful in the diagnosis of malignancy.

Signs of hepatic decompensation:

Cirrhosis patients seek medical attention for many reasons, some are specific for liver while others are not. Liver cirrhosis is said to be decompensated if the patient has any one of the following features,

. Raised serum bilirubin or clinical jaundice indicates damage is beyond the regenerating capacity of the liver,

. Upper gastrointestinal bleeding in the form of either haematemesis or malena.

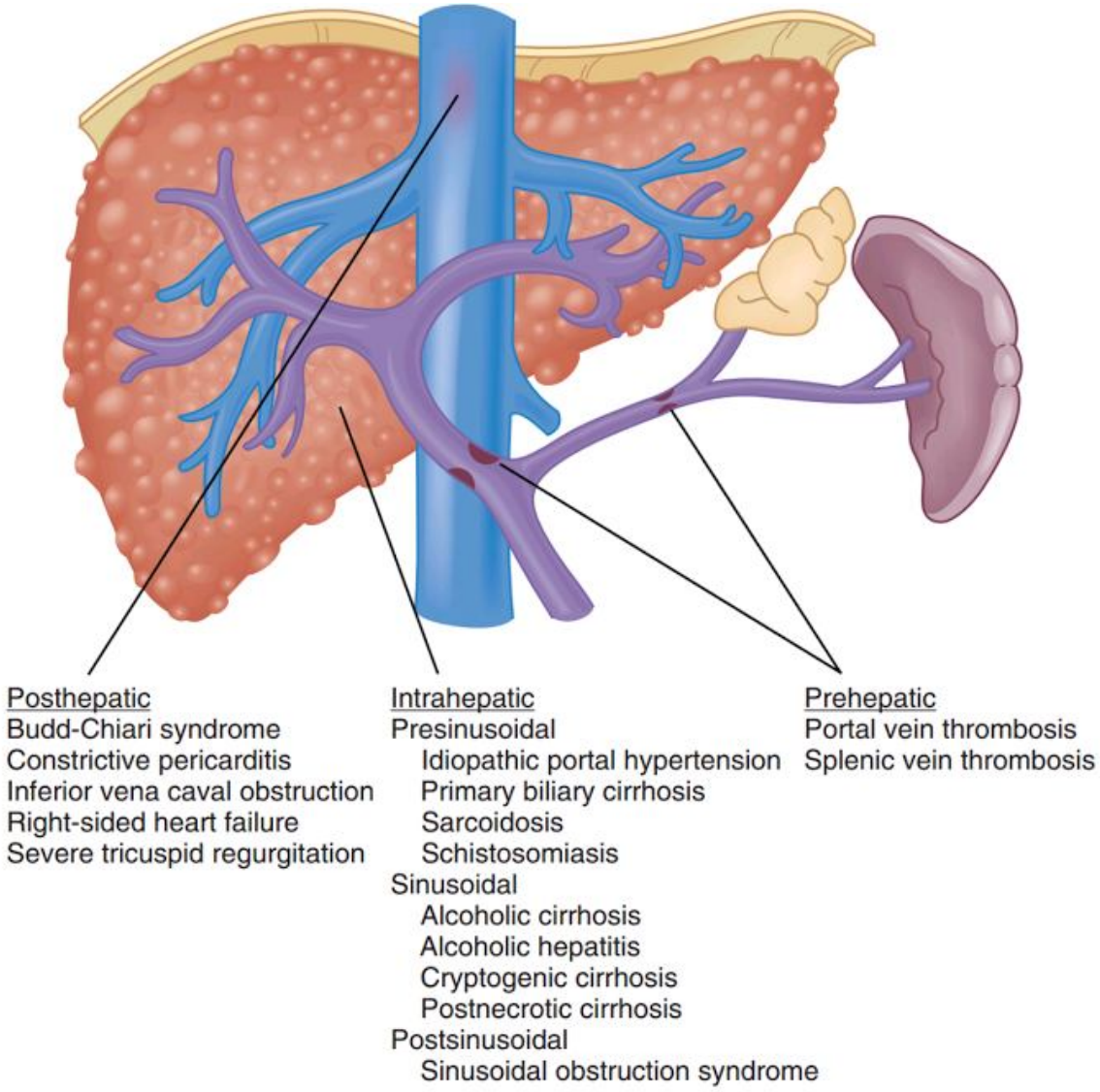


FIGURE 16 – CAUSES OF PORTAL HYPERTENSION

Ascites associated with or without abdominal tenderness and fever indicating spontaneous bacterial peritonitis,

- Ascites is the initial sign in most of the patients.
- Hepatic encephalopathy
- Hyponatremia, and renal failure {Hepato Renal syndrome}

Other associated factors that may are may not present in a decompensated state are, Generalized weakness, continuous fever which is of low grade, flapping tremors, hypotension, loss of secondary sexual characters, and bleeding manifestations in the form of purpura etc. due to low platelet count due to various reasons predominantly hypersplenism.

None of the above said signs are present in compensated cirrhosis, and it may be diagnosed in routine clinical examination for some other cause. Patient may have spider angioma, pedal edemaetc, that may indicate liver disease.

These patients enter decompensated state at the rate of approximately 10 % every year.

In decompensated liver disease 50% patients survive at the end of 18 months, but in compensated liver disease 50% patients survive at the end of 10 years.

Liver decompensation is an indication for transplantation of liver.

Pathophysiolgy of decompensation[48] and hyperdynamic nature of systemic circulation.

Systemic vasodilatation plays an important role in the manifestations of CLD. This occurs chiefly because of reduced response of the arteries to systemic vasoconstricting agents. Because of this the effective blood volume within the arterial tree is reduced leading to the activation of RAS system leading to retention of salt and water, that contributes to the formation of pedal edema , ascites and anasarca. All these factors leads to poor utilization of oxygen by the body.

Because of the generalized vasodilated state, a number of arteriovenous anastomosis are opened. The vasodilators include nitric oxide and prostaglandins. Nitic oxide explains lot of concepts, like the role of endotoxins produced by liver, which act by stimulation of NO synthase. And also inhibitors of NO release like L-ARGININE shows improvement in hyperdynamic circulation clinically.

All these changes get reverted [45,46,47]after liver transplantation ,except the elevated cardiac index and increased splanchnic circulation which takes longer to get normalized.

Prognostic scores of liver cirrhosis:

Child-pugh score: Mainly useful in assessing the prognosis in short term.

Modified Child's Classification

Variables	*Scores*		
	1	*2*	*3*
Encephalopathy (degree)	Nil	Slight-moderate	Moderate-severe
Ascites (degree)	Nil	Slight	Moderate-severe
Bilirubin (mg/dl)	< 2	2–3	> 3
Albumin (gm/dl)	≥ 3.5	2.8–3.4	< 2.8
Prothrombin index (%)	> 70	40–70	< 40
Prothrombin time (in seconds)	≤ 14	15–17	≥ 18

Scores are summed to determine Child's class.
Class A 5–7 (suitable for surgery)
Class B 7–10 (marginal risk for surgery)
Class C more than 10 (unsuitable for surgery).

FIGURE 17 – CHILD PUGH SCORE

It also guides in the therapy and also gives an ideaabout the need and timing of liver transplantation.

MELD SCORE:{ Model for End stage Liver Disease}

Variables used are

- Serum Bilirubin levels
- PT {PROTHROMBIN TIME}
- Serum creatinine levels

MELD score is very useful in prioritising the candidates for liver transplantation. MELD scoresexactly predict the mortality in waiting list for liver transplantation.

MELD = 3.78*SERUM BILIRUBIN[mg/dl]+11.2{INR}+9.57{SERUM CREATININE[MG/DL]}+6.43.

Serum sodium levels when used along with this, can improve the efficacy of the score.

UKELD:

It is a scoring system produced in United Kingdom. The variables used are

- INR
- SERUM Bilirubin levels
- Serum creatinine levels
- Serum sodium levels

This scoring system is very much comparable to MELD..

MADDREY'S DISCRIMINANT FUNCTION:

It is an example of scoring system that is highly specific for certain disease conditions, in this case hepatitis of alcoholic[49]etiology.

DF = SERUM BILIRUBIN /17 + PROLONGATION OF PROTHROMBIN TIME IN SECONDS WHICH IS COMPARED WITH CONTROL VALUES*4.6.

A maddrey's discrimannt value of more than 32 is a sign of poor prognosis and associated with increased rate of mortality {between 30 to 50%}within the hospital.

- Bad clinical markers in Liver disease:

- Spontaneous decompensated liver disease
- Poor response to theraphy at the end of 1 month of treatment
- Jaundice indicates severe underlying organ problem
- Autonomic neuropathy and chronic HE, indicate serious problem
- Diuretic resistant ascites
- Small shrunken liver that is not palpable
- Upper gastrointestinal bleed of variceal origin
- Prolonged state of low BP.

Clinical features of Cirrhosis:

GIT:

- Parotid gland enlargement, pancreatitis with calcifications, usually chronic in duration.
- Pigmented gall stones for which surgery is not usually advisible,
- Hernia usually Umbilical, for which surgery is not indicated unless there is a strong clinical indication.
- Duodenal and Gastric ulcers with predominantly caused by H.pyori infection.
- Enlargement of the spleen, usually moderate in size,
- Dilated veins over the abdominal wall, with flow away from the umbilicus indicating increased portal pressure.

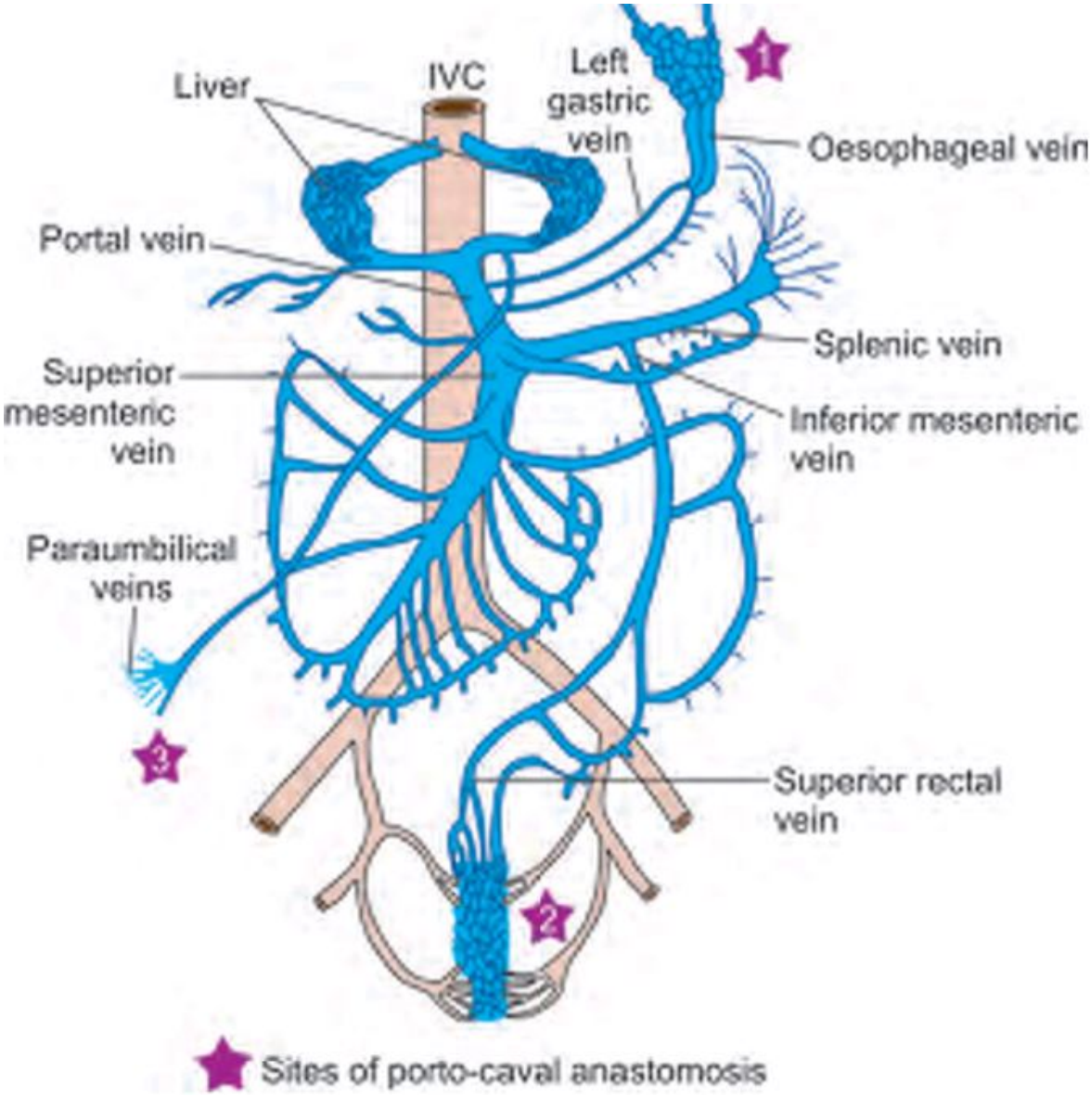


FIGURE 18 – PORTAL VENOUS SYSTEM

Urinary system:

.Glomerulonephritis, usually of membrano proliferative type.

- IgA[33,34] nephropathy

- Hepatic failure induced renal failure, especially because of the reduced blood flow to the cortex, known as Hepatorenal syndrome type 1 & 2, in which type 1 carries a very bad prognosis.

Patient has a faecal smell of breath that can have a slight sweetish component, occurs in some of the patients, it usually arises from the intestine. It reduces in intensity after passing stools with laxatives and after administration of antibiotics. It is caused by dimethyl ketones[52]. This clinical condition is called foetor Hepaticus and it is particularly useful in the assessment of a patient presenting with coma for the very first time.

Spider Angiomas are one of the markers of liver disease, it has a an arteriole in the centre, and few arterioles radiate from the centre. It is usually less than 5mm. It is examined by the glass slide test that reveals blanching. They indicate progression or regression of the disease with respect to their numbers. Their association with pan digital clubbing may be an manifestation of an associated pulmonary involvement known as hepato-pulmonary syndrome.

They usually occur in the upper part of the body in the territory of drainage of SVC. Common areas include face, neck , hand especially the dorsal part. They are more common with alcoholic etiology of liver cirrhosis than other causes for unknown reasons. They are physiologically present in children and during pregnancy and those will disappear spontaneously. Alarming Increase in size or number should be carefully followed up.

Palmar erythema:

Reddish dicolouration of the palms especially over the thenar and hypothenar areas, associated with blanching. They may occur physiologically in some families and also during cirrhosis. Other conditions associated with palmar erythema are hyperthyroidism, Autoimmune conditions like RA, fever of unknown origin and haematological malignancies .

The probable cause of these skin manifestations associated with cirrhosis is proposed to be an elevated levels of estrogen. It is the same reason because of which ,these changes occur in preganancy. Liver is the site of inactivation of estrogens. An increasing values of estrogen to testosterone levels are found in cirhotic {male} patients.

PEM:

Protein deficiency is common in cirrhosis patients. It is one of the poor prognostic indicators. It is caused by both increased energy loss and reduced food intake. They have low fat in the body and severe loss of muscle density. Ciirrhotics, especially of alcoholic etiology exhibit muscle weakness more than others. Status of the nutrition of the individual can be assessed by number of tests that includes mid arm circumference etc.

Hyperglycaemia is prevalent especially in NASH, when compares to other etiologies.

Secondary sexual characters:

Testicular atrophy, loss of axillary and pubic hair , impotence and reduced sexual drive can occur in cirrhotic patients , especially of alcoholic etiology.

In females there is menstrual disturbances , loss of breast volume, and increased prevalence of infertility. These sexual changes are usually not found in women with NASH.

Enlargement and tenderness of the breast in male known as gynaecomastia occurs commonly with spironolactone therapy. It occurs mainly because of reduction in the circulating testosterone levels and again like many other previously mentioned abnormalities is more common in cirrhosis of alcoholic etiology.

The main mechanism of above mentioned changes is the hepatic downregulation of androgenic receptors and upregulation of estrogen receptors.

Ocular manifestations:

Retraction of the eyelid and lag of eyelids can be seen in cirrhosis patients. These patients have a normal thyroid functions.

Muscle cramps occurring in cirrhotic patients is a common occurrence and can be treated with quinine salts p.o

Metabolism of majority of drugs are altered in hepatic cirrhosis. It is mainly attributed to loss of hepatocytes. The dosage of most of the drugs should be reduced.

Evaluation of Lab parameters:

Anaemia may be normocytic or macrocytic. Increased MCV usually occurs in alcoholics due to vitamin b12 and folate deficiency. Hypochromia is mainly because of blood loss.

Splenic sequestration of white blood cells and platelets occurs leading to leucopenia and thrombocytopenia. This is known as hyperspleenism

PT is prolonged and is not corrected by Vitamin K therapy.

There is a fall in the albumin levels that indicates the synthetic function of the liver, and that of gamma globulin is increased, leading to reversal of AG Ratio. Raised globulin is due to increased production of antibodies in response to the antigens against intestinal antigens. Serum ALT and AST levels are only mildly increased compared to ALP levels , which are markedly elevated.

Urinary picture shows an elevated urobilinogen and sometimes conjugated biliorubin may be present in case the patient is icteric, and in case patient has ascites urinary excretion of sodium very much compromised.

Cirrhotic patients are more prone for infections when compared to general population. SBP is a common occurance in ascites patients. Meningitis caused by bacteria is one of the possibilities in a cirrhotic patient with coma.

Sepsis is the most common cause of unexplained fever in cirrhotic patients. They should be treated with antibiotics with wide coverage until culture results become available. Routine prophylaxis with antibiotics is practised now.

Pneumonia, endocarditis, urinary tract infections all can occur in cirrhotic patients.

Hospital acquired infections are more dangerous as they are caused by resistant organisms, when compared to community acquired infections.

Lung involvement:

In patients with cirrhosis , there is a low oxygen saturation in some patients. This is known as the hepatopulmonary syndrome. In the above said patients there is no known previous cardiac or pulmonary abnormality. This occurs because of dilatation of the lung vascular tree. Breathlessness relieved by lying down flat and aggravated by sitting upright is a common mode of presentation. It does not reflect the severity of the disease, but it is associated with increased mortality. No definitive therapy is available for this condition, liver transplantation is the only available option. TIPS may be useful in some of the patients.

Management :

The management is only symptomatic. Complete cure cannot be obtained.

The main goal of management in case of compensated liver failure is for abstinence from alcohol , lifestyle modification, and being watchful for the signs of development of ascites , malignancy [primary HCC], and development of neuropsychiatric manifestations known as hepatic encephalopathy, hepato-renal syndrome and prevention of upper gastrointestinal bleeding.

In decompensated state the, management is mainly concentrated in correcting the cause of the decompensation. Usually there will be a precipitating factor that would have predisposed to the decompensated state, treatment is mainly depends upon finding out the correct predisposing factor and correction of the same. Some of the examples are sepsis, drugs UGI bleed etc.

Specific condition	Treatment
Viral hepatitis B and C	Antivirals
Autoimmune Hepatitis	Steroids , immunosuppressive agents
Primary biliary cirrhosis	UDCA, early phase of the treatment.
Wilsons disease	Chelation theraphy
Haemochromatosis	Venesection.

TABLE 2 - SPECIFIC TREATMENT FOR DIFFERENT CAUSES OF CIRRRHOSIS

Nutritional Management:

Cirrhotics are more prone for malnutrition and protein deficiency, they cannot tolerate minimal intervals of fasting. They should take atleast40 kilocalories of energy and 1.5 gram of protein per kilogram of body weight. Reducing the intake of fats doesn’t carry any therapeutic value. Protein restricted diet when used, especially in the setting of HE, should only for short duration. feeding of food in night between 9.00pm and morning 7.00am is shown to be beneficial.

Any Operative procedures have an increased chance of mortality, both intra-operative and postoperatively. The main factors, that should be taken into account are the serum albumin levels, infection, and bleeding tendency reflected by prolongation of PT.

HEPATIC ENCEPHALOPATHY:

HE signifies the alterations in the neurological and psychiatric status of a cirrhotic patient. This causes a negative impact on quality of life especially health related and on survival of the patient. It is an complex interplay between failure of hepatocytes and shunting between systemic and portal circulation. Ammonia derived from the intestine enters the systemic circulation bypassing the detoxifying effect of the liver and in turn detoxified by the astrocytes of the brain. This leads to oedema of the brain and the entire spectrum of the clinical manifestations.

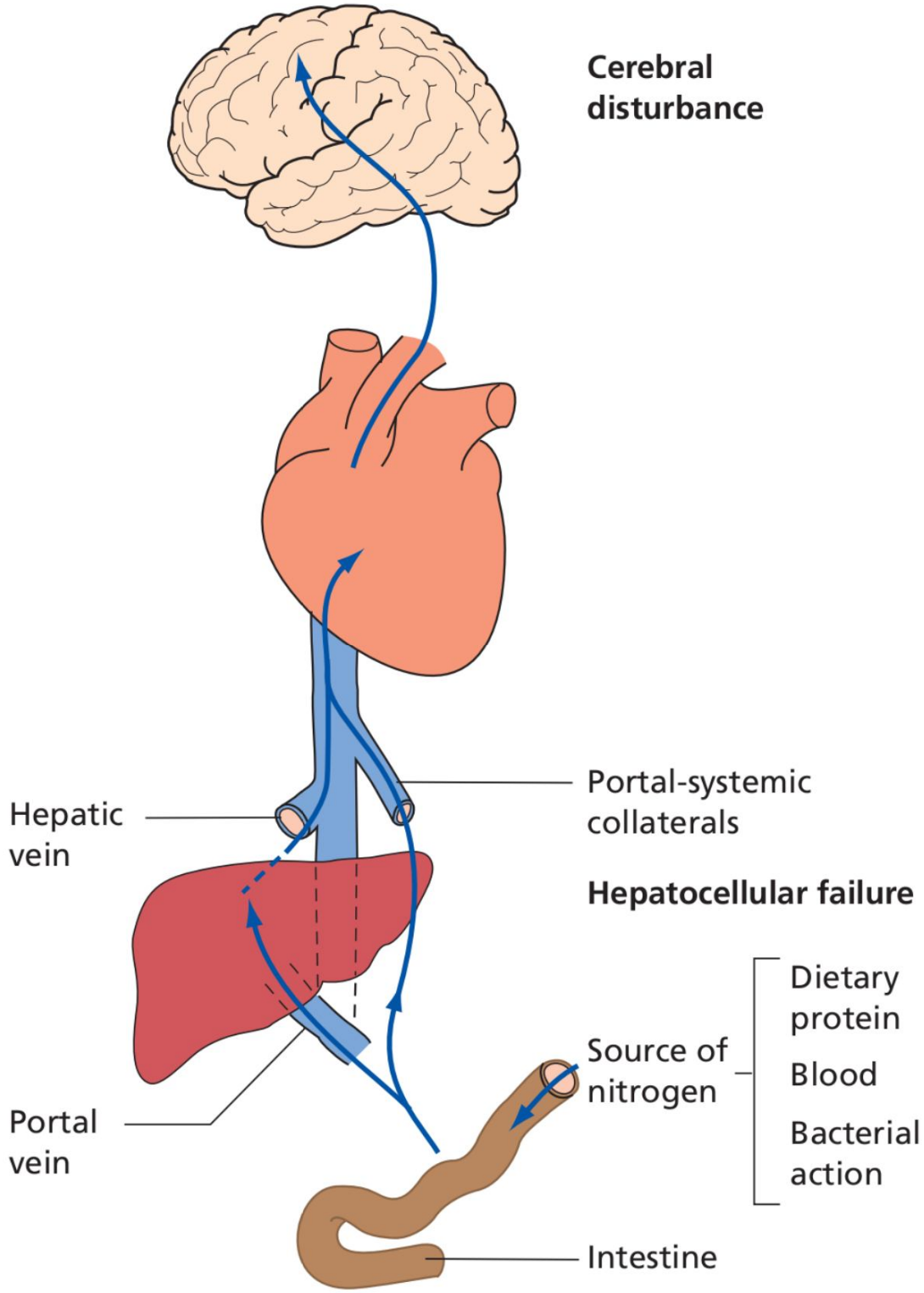


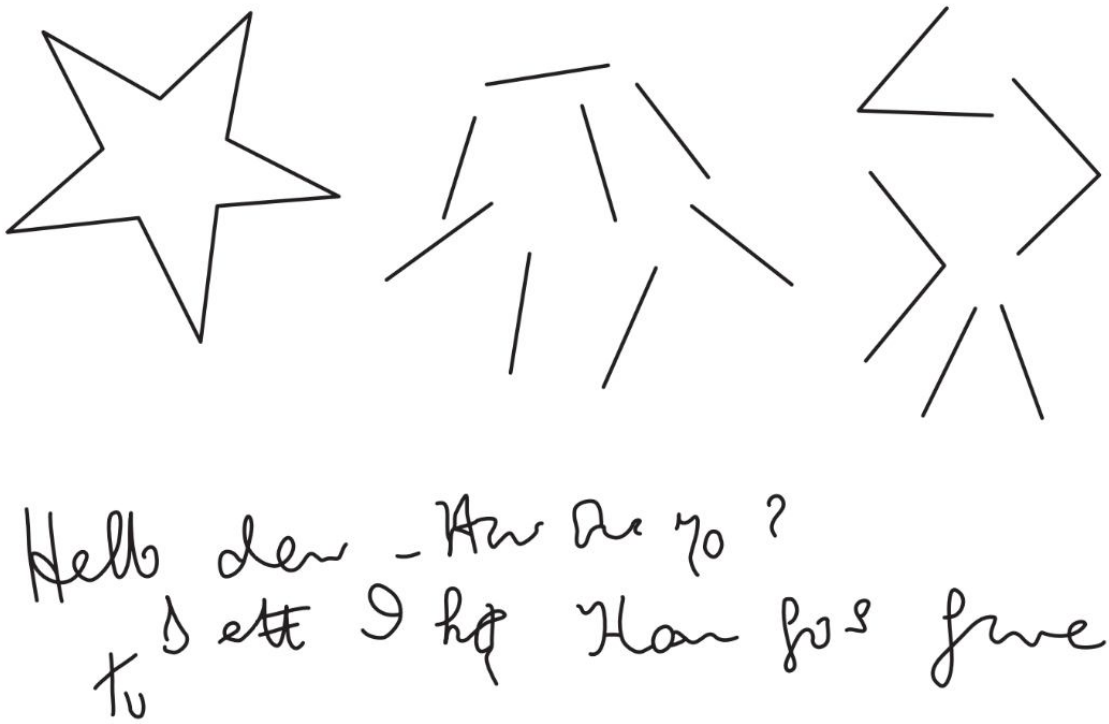
FIGURE 19 – MECHANISM OF HEPATIC ENCEPHALOPATHY

Clinical types:

Overt HE:

This is a clinically apparent form of HE. This may be continuous and stable or episodic. Changes in mentation[53,54] includes a wide range from mild personality disorders to comatose state. Childish behaviour getting easily irritated, and lack of affection for family members are due to personality disorders. Intellect is impaired to varying degrees, ranging from mild to severe confusion. Visual spatial impairment may occur even in stable mentation. It manifest as inability to redraw simple diagrams like stars, known as constructional apraxia.

FIGURE 20 – CONSTRUCTIONAL APRAXIA



Disturbance of sleep pattern is commonly observed in the form daytime sleepiness and disturbed night sleepiness. Hepatic coma, in the initial stages, mimics

normal sleep, but then progresses to a state in which, the patient responds only to very intense stimuli.

Foetor hepaticus is present in some cases of HE[55],but its presence is not an essentiality and it doesn't the severity of HE.

Motor abnormalities include hypertonia in the form of rigidity, aphasia, tremor both in resting and movement related, diminished and exaggerated reflexes, extensor plantar reflexes, etc.

Flapping tremor {asterixis}:

It is due to impaired afferent impulses from joints to reticular system of the brain stem. It is best appreciated in a posture that is sustained for sometime. Example in an outstretched hand. It is usually bilateral but may not be symmetrical. Other equivalent tests are the movements seen in neck, arms . It is also seen on protrusion of the tongue and on tightly closing the eyelids. All said asterixis is not only seen in HE, but also in other conditions like failure of heart, renal and respiratory systems, and electrolyte abnormalities like reduced magnesium levels.

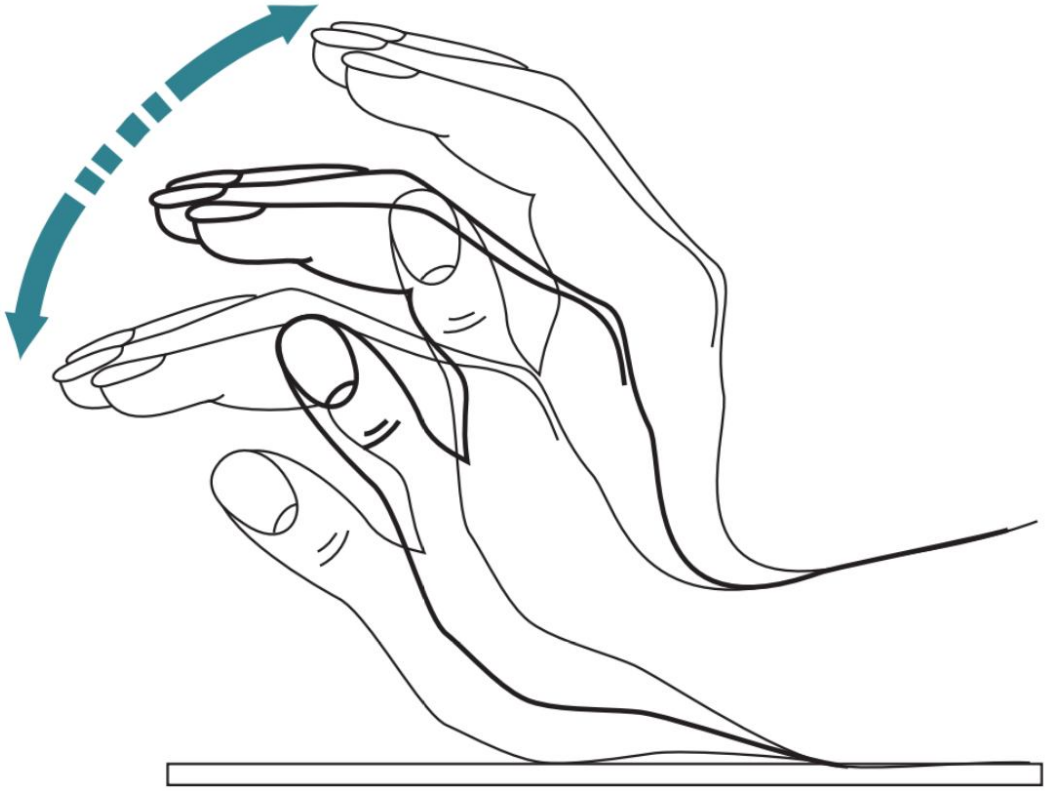


FIGURE 21 – FLAPPING TREMOR

Other neurological abnormalities observed are slurring of speech, exaggerated DTR, hypertonia and clonus.

Episodic HE:

This conditions usually occurs in previously stable patients. In most of the patients, the precipitating factor can be found out. The mechanism involved are

- Compromising an already impaired hepatic function and/or cerebral function.
- Sudden increase in the load of nitrogenous substances.
- Onset of an inflammation cascade.

Precipitating event	Effect
Upper gastrointestinal bleeding Misuse of higher dose of Diuretics Huge volume ascitic tapping Loose stools	Perfusion of liver is reduced due to loss of fluids
Upper gastrointestinal bleeding Protein rich diet Constipation	Nitrogen delivery to liver is increased
Infection inflammation alcohol ingestion, drugs TIPS	Suppresses the cerebral function.

TABLE 3 - PRECIPITATING FEATURE OF HE

Persistent HE:

In this group of patients there is continuous HE. In these patients, invariably porto-systemic shunting is present. Extrapyramidal features maybe present. cerebellar features are also found. The clinical picture may predominantly reflect a neuropsychiatric disorder and evidence of liver disease is subtle. It makes the diagnosis, a bit difficult.

Minimal HE:

These patients are clinically without any abnormalities but have mild cognitive impairment.[56,57]

Diagnosis of HE:

The diagnosis of HE in a known case of CLD, presenting with altered mentation, asterexis is straight forward. The absence of these details make the diagnosis challenging.

MSE and CNS EXAMINATION.

Grade	Feature
0	No abnormalities detected
1	mild anxious state, reduced attention.
2	Lethargy, lack of orientation to time, personality disorders,lack of affect.
3	Increased somnolescence, severe disorientation,
4	Coma

TABLE 4 - WEST HAVEN CRITERIA:

Variable	Score
Eye open	
Spontaneously	4
To command	3
To pain	2
No response	1
Best motor response	
Obeys verbal commands	6
Painful stimulus, localizes pain	5
Painful stimulus, flexion/ withdrawal response	4
Painful stimulus, abnormal flexion	3
Painful stimulus, extension	2
No response	1
Best verbal response	
Orientated and conversant	5
Disorientated and conversant	4
Inappropriate words	3
Incomprehensible sounds	2
No response	1
Total score	3 (Worst) to 15 (Best)

FIGURE 22 - GLASCOW COMA SCALE:

Psychometric analysis:[58,59]

Affected patients have minimal HE, but appear normal otherwise on clinical examination. In patients with obvious clinical features of encephalopathy it helps us to measure the degree of impairment. The tests commonly employed are connecting the numbers, tracing the lines etc. psychometric analysis with computers are also available.

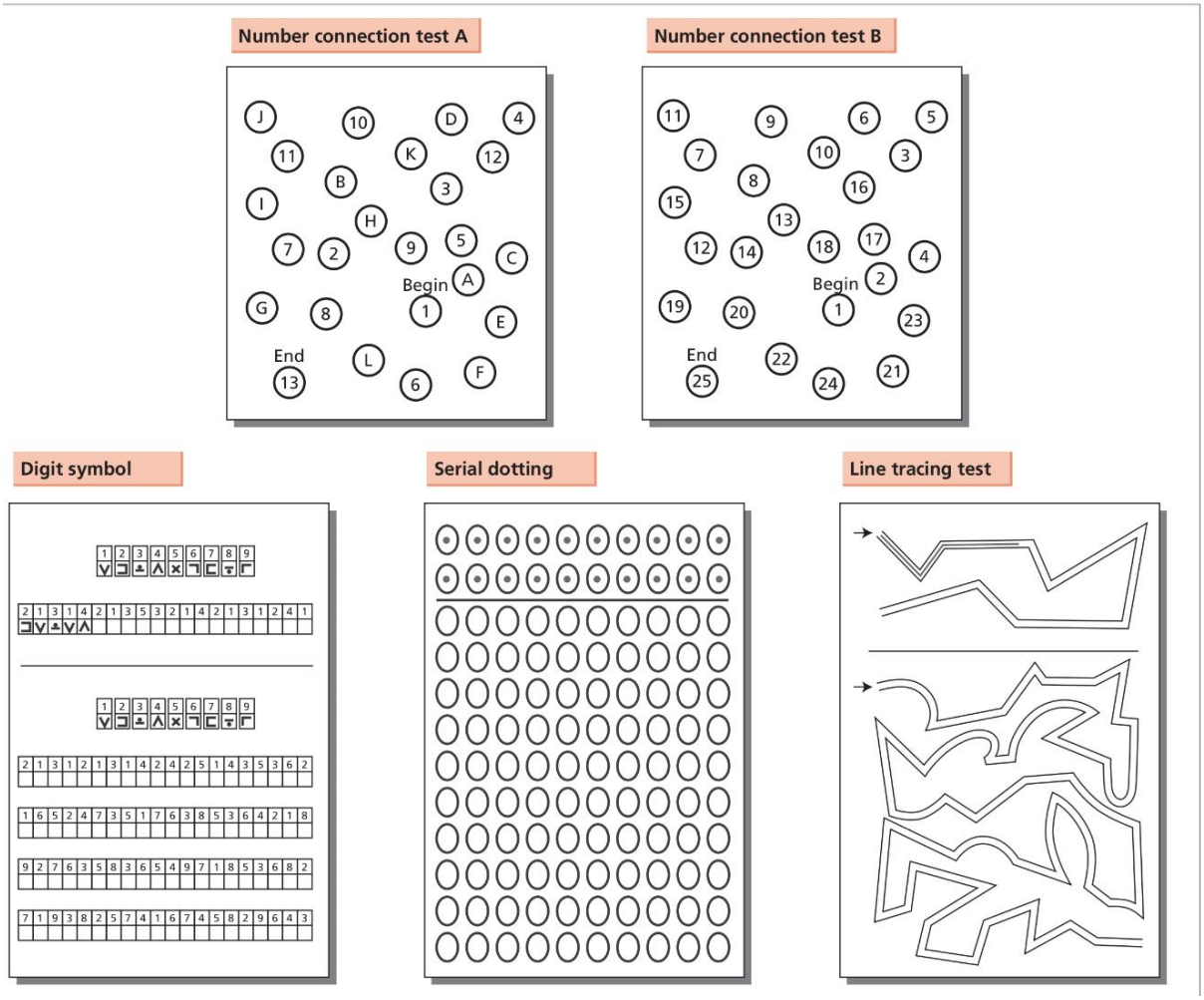


FIGURE 23 – PSYCHOMETRIC ANALYSIS IN HE

EEG:

EEG analyse the neuronal activity in the brain cortex. In HE there is usually slowness ,that is progressive in nature. This is not only seen in HE, but also in number of other conditions including electrolyte abnormalities, etc, but all these conditions can be distinguished on the basis of a clear history and clinical evaluation.

Radiological modalities:

Radiological investigations like CT and MRI, mainly helps us to rule out other possible causes, they are not helpful in diagnosing a case of HE. There may be atrophy of the cerebral hemispheres, especially more common in alcoholic cirrhosis, and increased intensity of basal ganglia. This explained as due to deposition of manganese that is produced because of the detoxification of ammonia by the cerebral astrocytes.

Ammonia measurement in blood:

This test is particularly useful in conditions where the patient is not a known cirrhotic, but presented with features of HE, and examination reveals very little evidence of liver disease. In this scenario ammonia [60]levels are of immense value and help in reaching definitive diagnosis. The partial pressure of ammonia in blood is more reliable than plasma levels of ammonia.

Cerebrospinal fluid Analysis:

CSF analysis is normal except for raised protein levels and increased glutamate levels Glutamate levels equate well with clinical profile of HE and the severity of HE[61].

Treatment:

HE is a condition that requires aggressive management. There are a lot of options and the combination of these should be used and individualized according to the patient. In patients with Hepatic cirrhosis, the first step is to identify and treat the precipitating factor, after this , prevention of future episode by prophylactic management should be done. Some of the common precipitating features are infections UGI bleed, electrolyte abnormalities, etc, these should be identified and corrected immediately.

Diet: cirrhotics have a very low glycogen, depend upon gluconeogenesis, which in turns upon amino-acids. Daily glucose consumption should be around 40 kilocalories/kg, and protein of 1.5 g/kg. Proteins of plant origin with high fibre content increases the ammonia excretion in faeces

Enema management: it is particularly very much useful in acute circumstances, but in patients with chronic HE, daily enema may be given. Lactulose is preferred. They act by three main ways.

- Reduces the transit time by laxative effect.
- Lactulose causes PH alterations in the lumen of the colon, that leads to the seepage of ammonia from systemic circulation

- Ammonia synthesis in the intestine is reduced.

It should given at a dose that is able to produce atleast 2 soft stools per day. Lactitol is more efficacious and better tolerated than lactulose.

Antibiotics: The main purpose of antibiotics is to kill the organisms that generate urease. Neomycin given per oral previously. it has the risk of developing oto and nephrotoxicity. Rifaximin is an synthetic drug that is equally effective as lactulose.

MATERIALS AND METHODS

SOURCE OF STUDY:

Data consists of primary data collected by the principal investigator directly from the patients visiting the Coimbatore Government Medical College Hospital.

DESIGN OF STUDY: Prospective Observational Study

PERIOD OF STUDY: One year, July 2015 - June 2016.

SAMPLE SIZE: 100

INCLUSION CRETERIA:

1. Patients (Both Genders) diagnosed as Liver cirrhosis at Coimbatore Medical College Hospital.
2. Age above 18 yrs.

EXCLUSION CRITERIA:

1. Presence of secondary immunodeficiency states- HIV
2. Hepatocellular cancer patients,
3. Patients on corticosteroids or cytotoxic drugs
4. Patients with ongoing Infection
5. Pregnancy and lactation
6. Patients not capable of giving consent (psychiatric patients).
7. Patients not willing to participate in the study (who refused to consent).

METHODOLOGY

Patients attending the Medicine and Gastroenterology outpatient department, who are known cases of cirrhosis of liver inspite of aetiology, who full-fill the inclusion and exclusion criteria are involved in the study after obtaining informed consent from the patients.

Blood samples from these patients are taken and sent for investigations. The investigations includes, Complete blood count and their neutrophil to lymphocyte ratio is calculated.

All these patients where followed up over a period of one year, through follow-up visits, follow-up during inpatient admissions for various reasons and through phone.

Patients Who Got admitted where thoroughly evaluated with investigations that includes,

- Complete Blood Count,
- Liver Function Tests,
- Serum Proteins,
- Serum Electrolytes,
- Renal Function Test,
- Ascitic Fluid analysis,

- Ultrasound Abdomen.

The patients in Follow-up, who got admitted in our GH where evaluvated for development complications, and patients who got admitted elsewhere where also followed up, through subsequent visits and Phone.

Among these patients, those who developed complications where identified and the correlation with the already calculated Neutrophil to Lymphocyte Ratio was done and the Results were analysed.

.

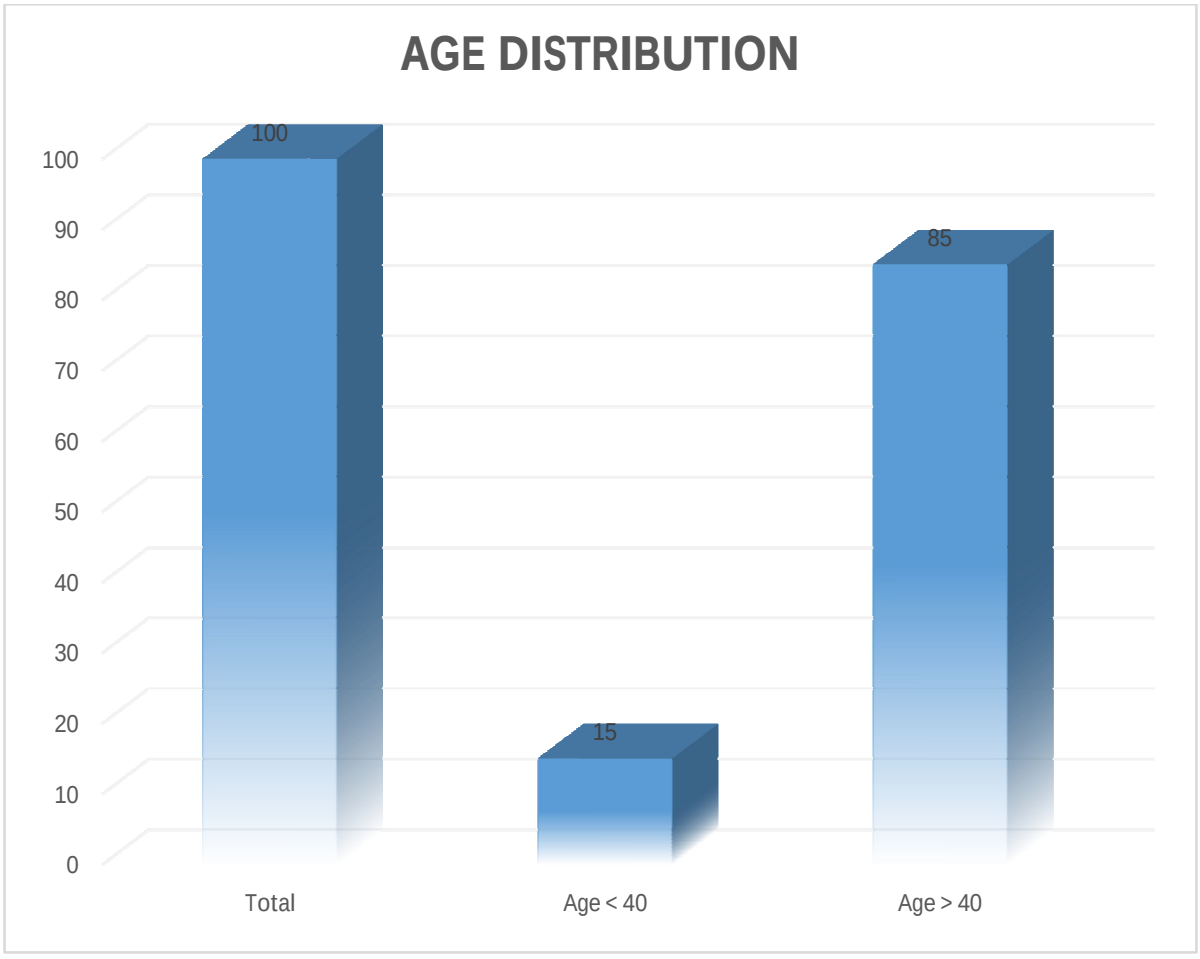
.

.

RESULTS AND ANALYSIS

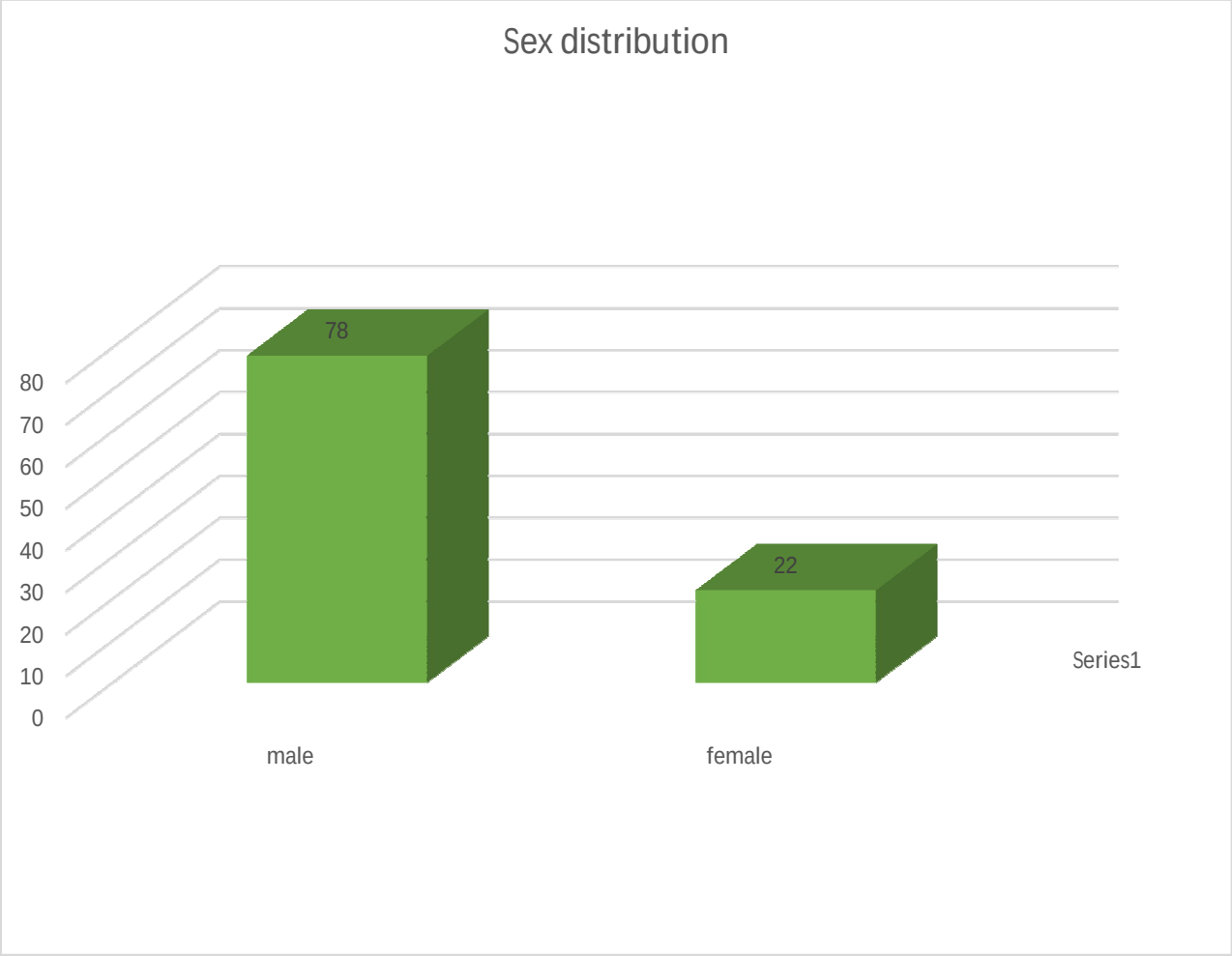
The study populations included 100 patients who have full filled the inclusion and exclusion criteria. Various characteristic patterns of the study population are analysed including age, sex distribution and alcohol consuming patterns.

CHART 1 – AGE DISTRIBUTION



Among the 100 patients, the study population predominantly consists of patients of age more than 40 years .

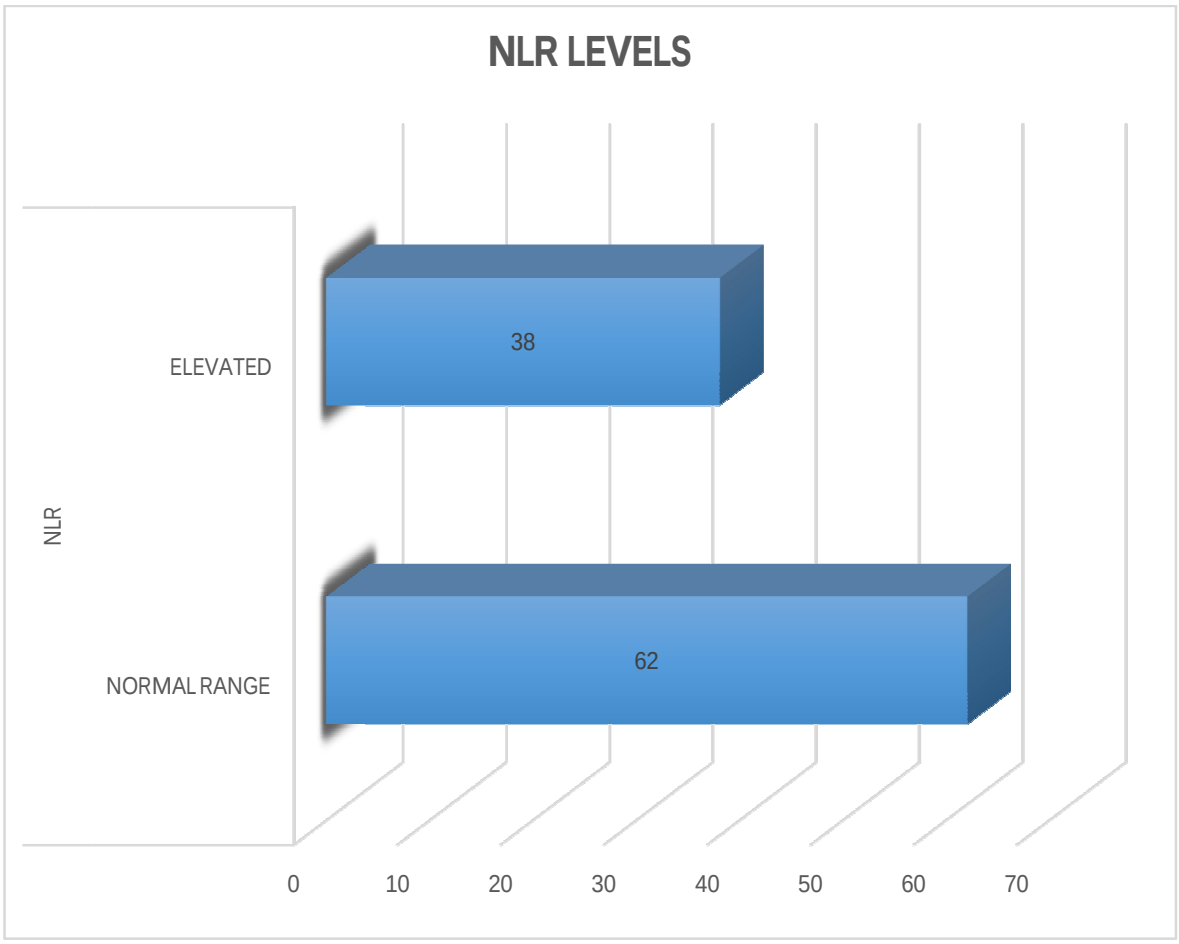
CHART 2 – SEX DISTRIBUTION



Among the study population, the predominant population is formed by males and a comparatively lesser population is formed by the females. This indicates the prevalence pattern of cirrhosis in general population.

Looking into the causes of such a distribution, alcoholism stands out as the prime factor that predisposes men to cirrhosis, as compared to their female counterparts.

CHART 3 – NLR LEVELS



NLR ratio is the ratio of absolute count of neutrophils to the absolute count of lymphocytes.

NLR ratio is calculated by dividing the absolute Neutrophil count by the absolute lymphocyte count.

The cut-off value of NLR is 2.72. The normal range group of patients have a NLR ratio of < 2.72 and the elevated group of patients have a NLR ratio of > 2.72.

CHART 4 – NLR STATISTICS

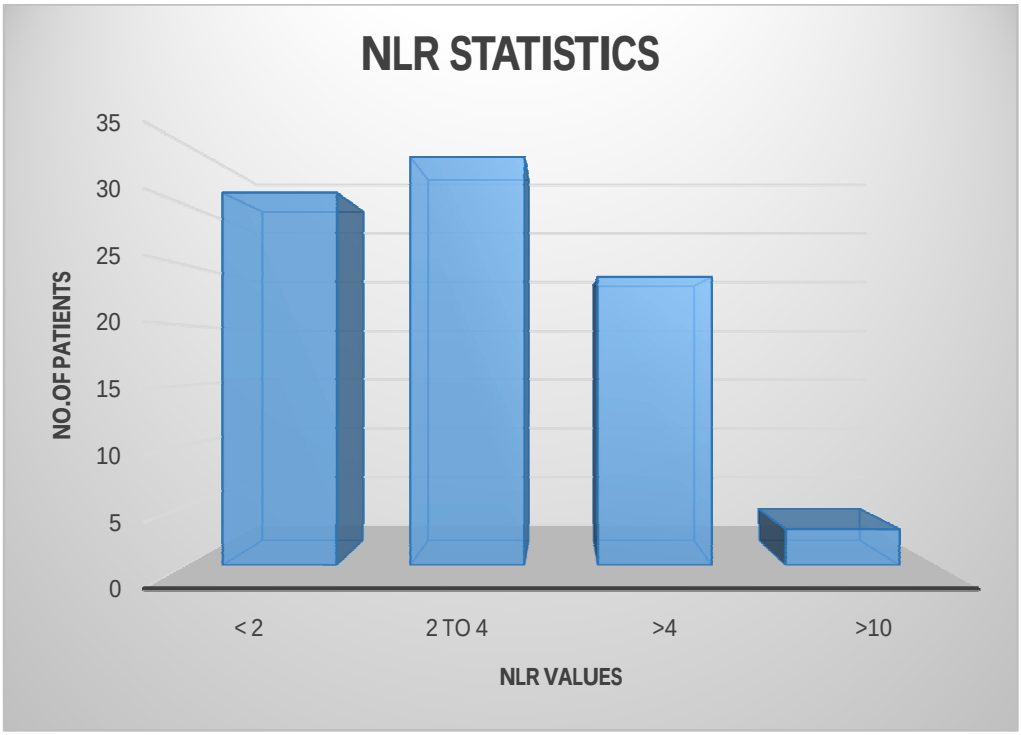
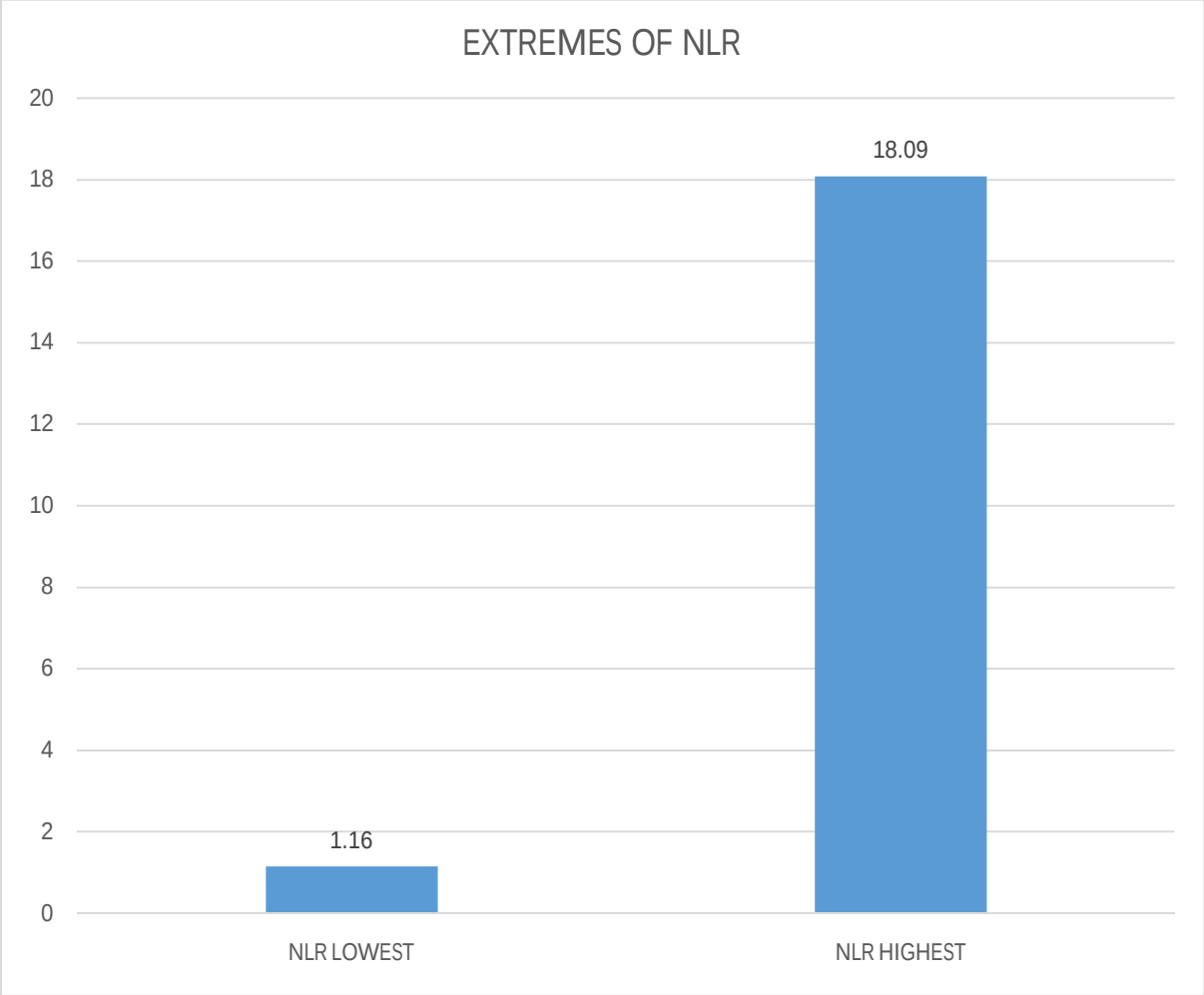


TABLE 5 – NLR DISTRIBUTION

NLR LEVELS	NO.OF PATIENTS
<2	31
2 TO 4	34
>4	24
>10	3

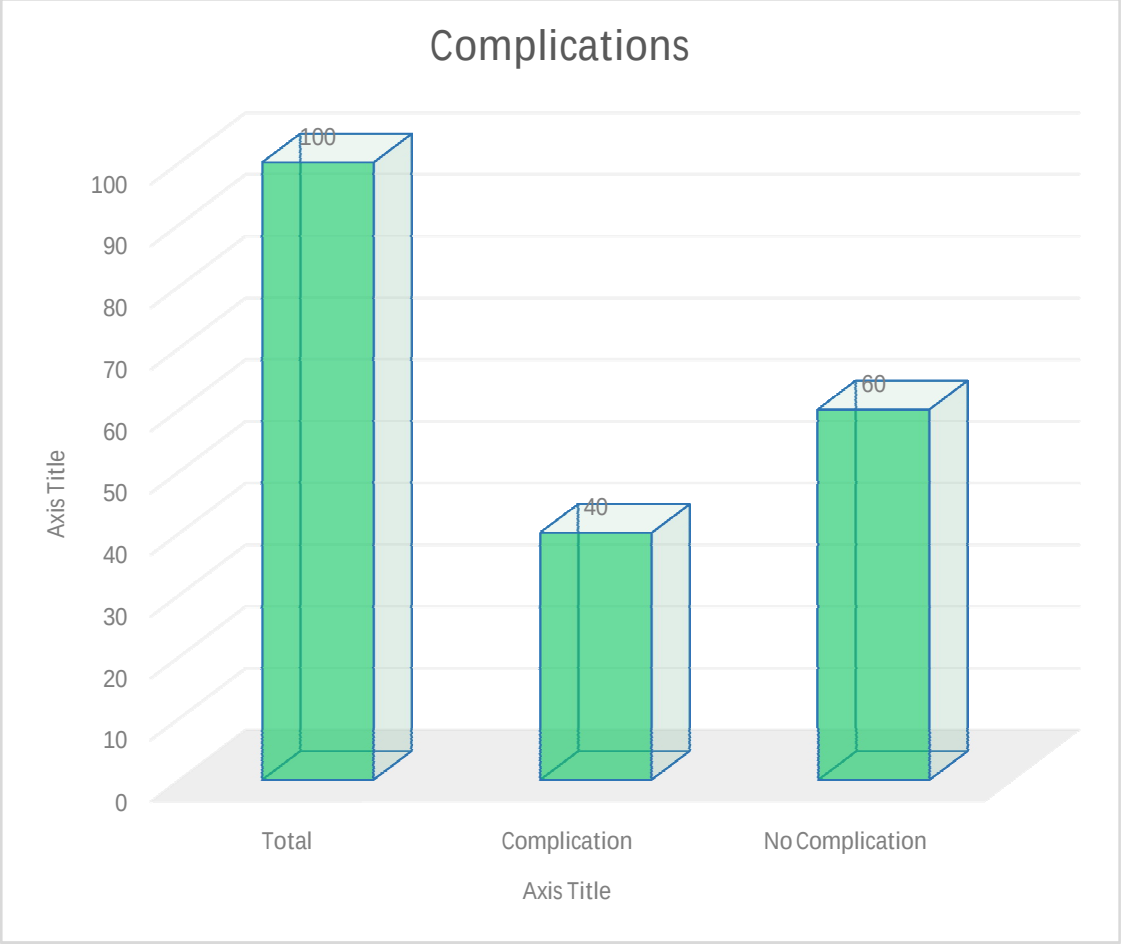
CHART 5 – NLR EXTREMES



The highest number of study subjects fell in the NLR range of 2 to 4. 3 patients had an NLR ratio of more than 10 and all 3 of them had more than one complication.

The lowest NLR recorded was 1.16 and the highest NLR obtained was 18.09.

CHART 6 – COMPLICATION PREVALENCE

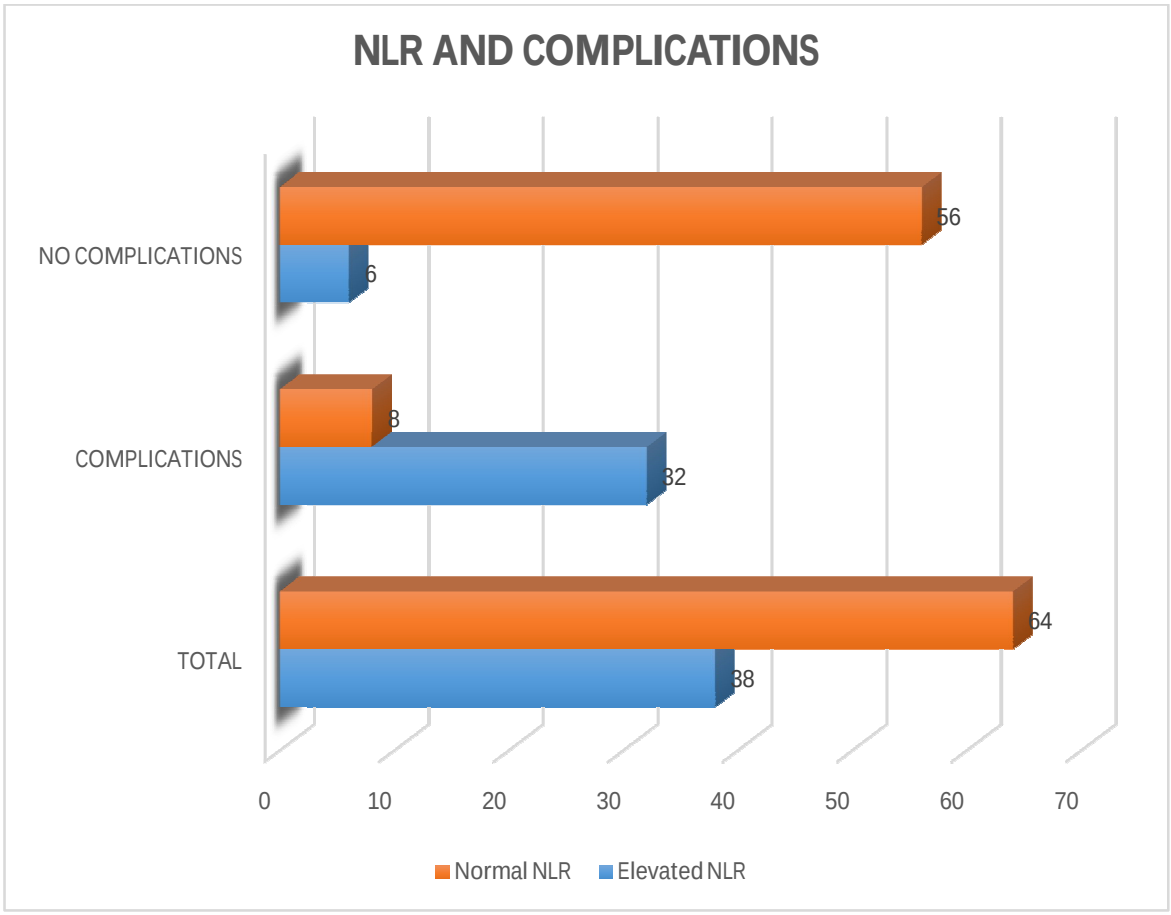


Among the total of 100 patients taken up for this study, 40 patients developed complications, in the due course of the study ie, 1 year.

The complications was more prevalent in the elevatedNLR group as compared to the normal NLR group.

The complications encountered include Upper gastrointestinal bleeding, Ascites and Hepatic Encephalopathy.

CHART 7 – NLR AND COMPLICATIONS



Among the 38 patients who had an elevated NLR ratio 32 developed complications and only 8 patients with normal NLR developed complications. We compared both the sample groups statistically.

TABLE 6 – NLR AND COMPLICATIONS

	High NLR	Normal NLR
TOTAL	38	62
COMPLICATION	32	8
NO COMPLICATIONS	6	54

RESULTS

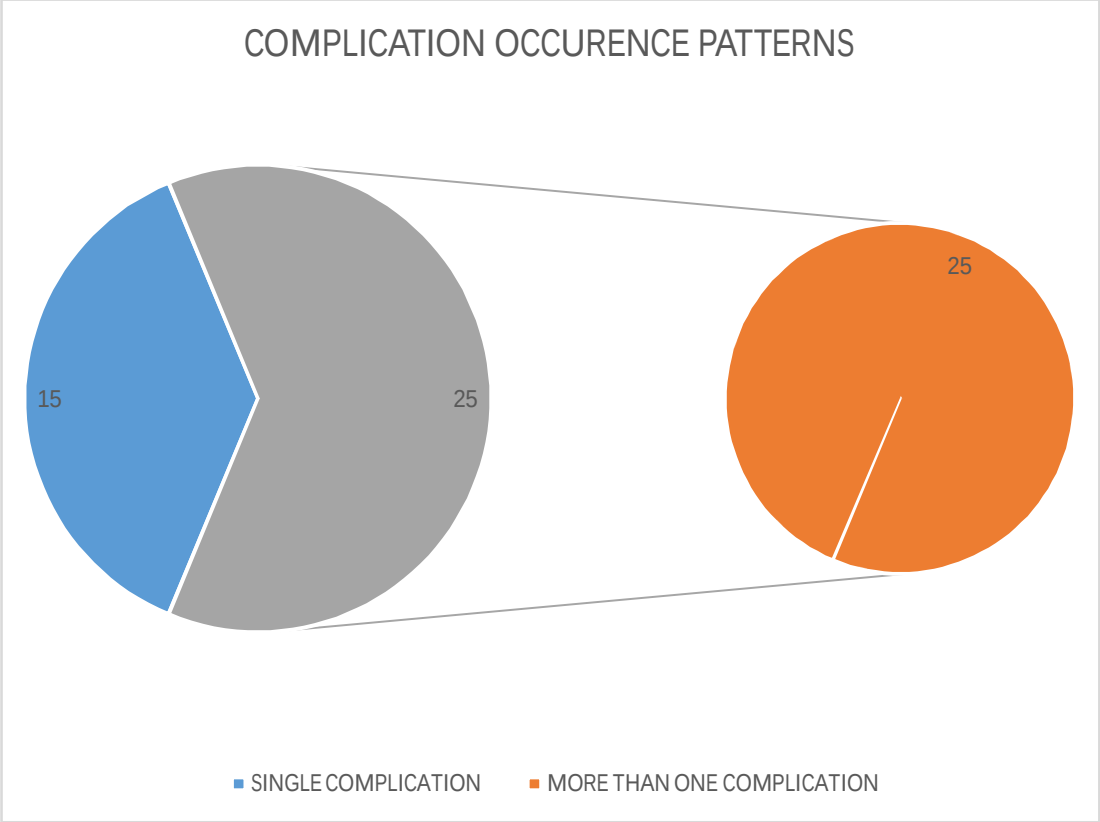
TABLE 7 – P VALUE CALCULATION

Difference	24%
95% CI	6.8126 to 41.9109
Chi-squared	9.468
DF	1
Significance level	P = 0.0021

The results show a P value of 0.0021 which is less than 0.05 and hence statistically highly significant.

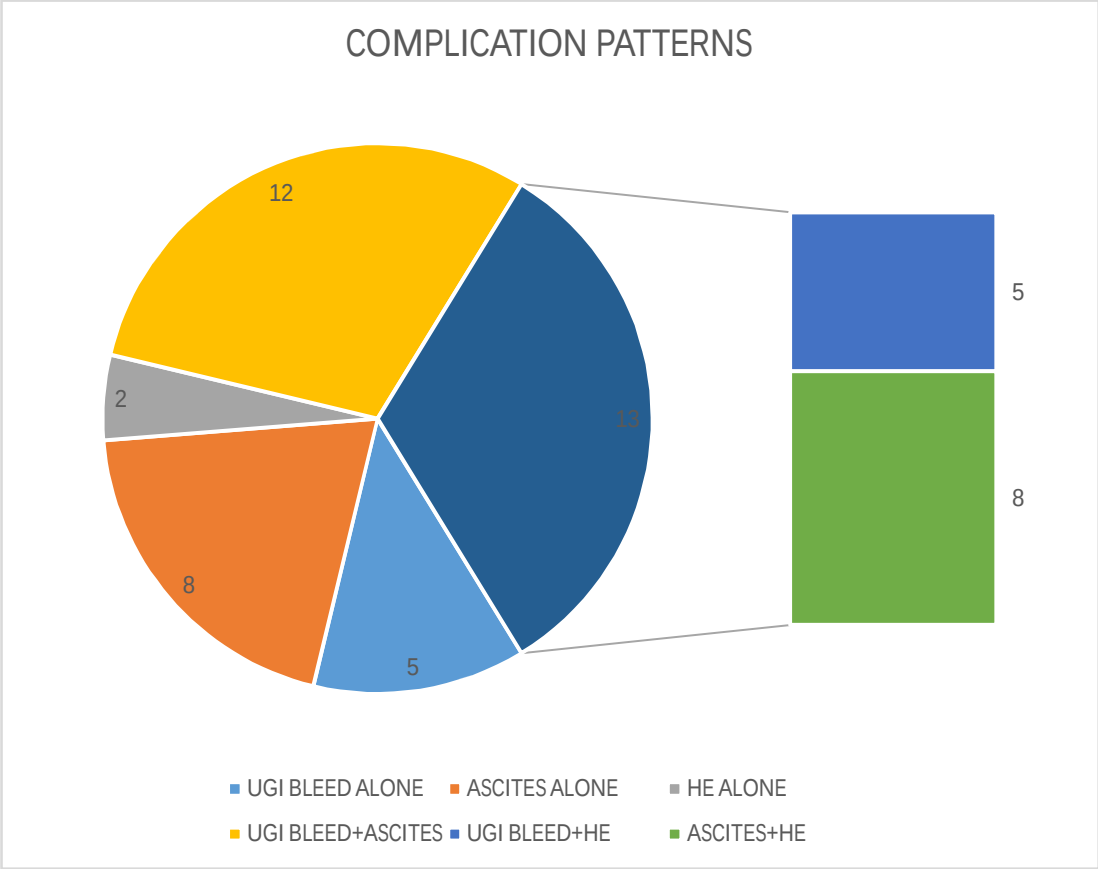
Hence this indicates High NLR is associated with higher incidence of development of complications.

CHART 8 – COMPLICATION OCCURRENCE PATTERNS



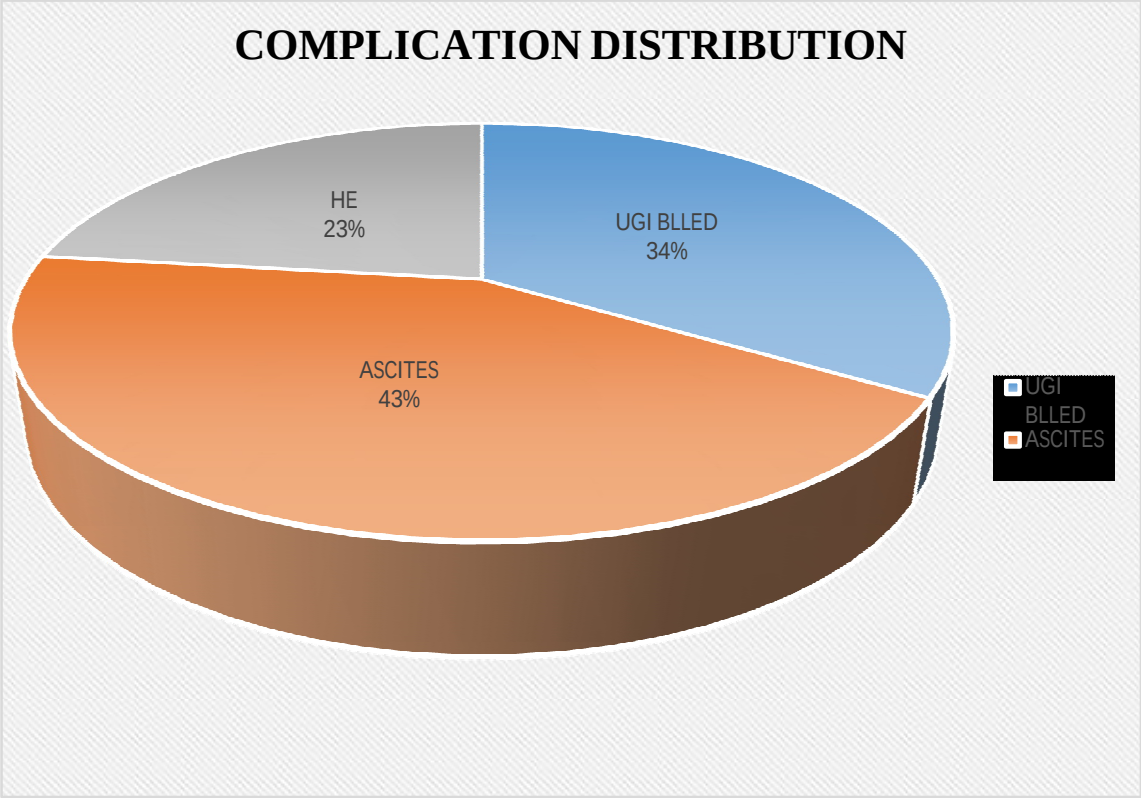
Among the study population the prevalence of complications was variable. A part of the population had a single complication, but a major part of the patients had a combination of the above said complication.

CHART 9 – COMPLICATIONS DISTRIBUTION



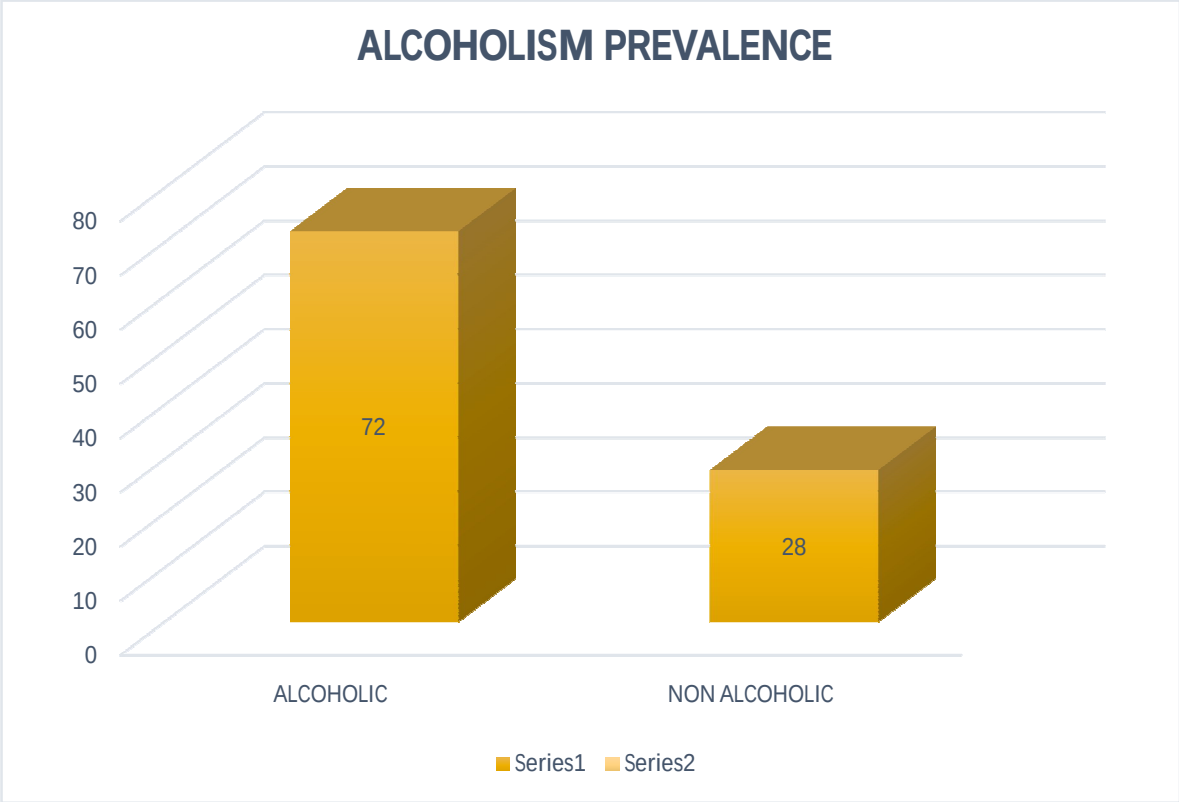
The occurrence of complications in the study populations had a variety of combinations. Part of them had a single complication and a majority of them had a combination, like Upper Gastrointestinal bleeding with Ascites, Ascites with Hepatic Encephalopathy and Upper Gastrointestinal Bleeding with Hepatic Encephalopathy.

CHART 10 – COMPLICATION PERCENTAGE DISTRIBUTION



Taking into consideration both the individual and combination occurrence of the complications, Ascites was the most Prevalent of the complication followed by UGI Bleed. The least prevalent of the complications was Hepatic encephalopathy compared to other complications in the study population.

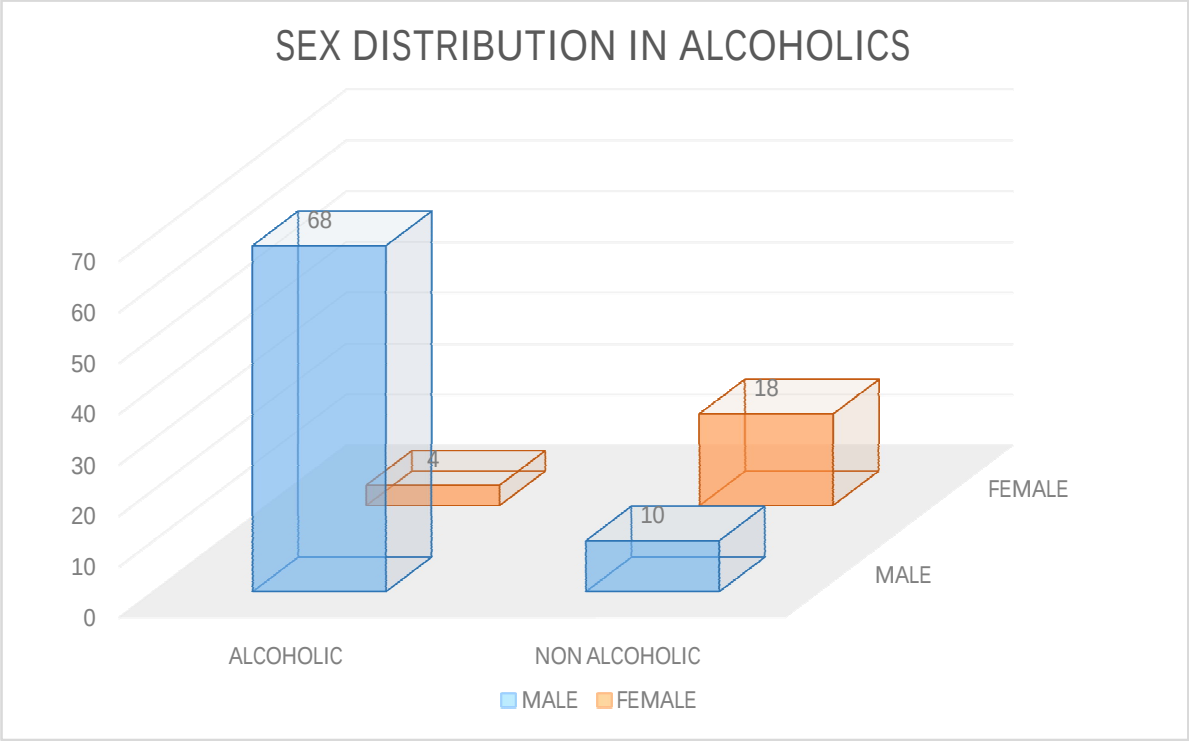
CHART 11 – ALCOHOLISM PREVALENCE



Alcoholism prevalence among the study population was high. Alcoholism is a very important factor because it itself can cause cirrhosis as an isolated cause and also can be an important co factor when it occurs with other causes of cirrhosis such as viral infections as it accelerates the process of the hepatic cirrhosis.

When compared to the western population, south-east Asians, especially the Indians more easily develop cirrhosis with relatively lesser amount of alcohol intake and with lesser duration of alcohol intake.

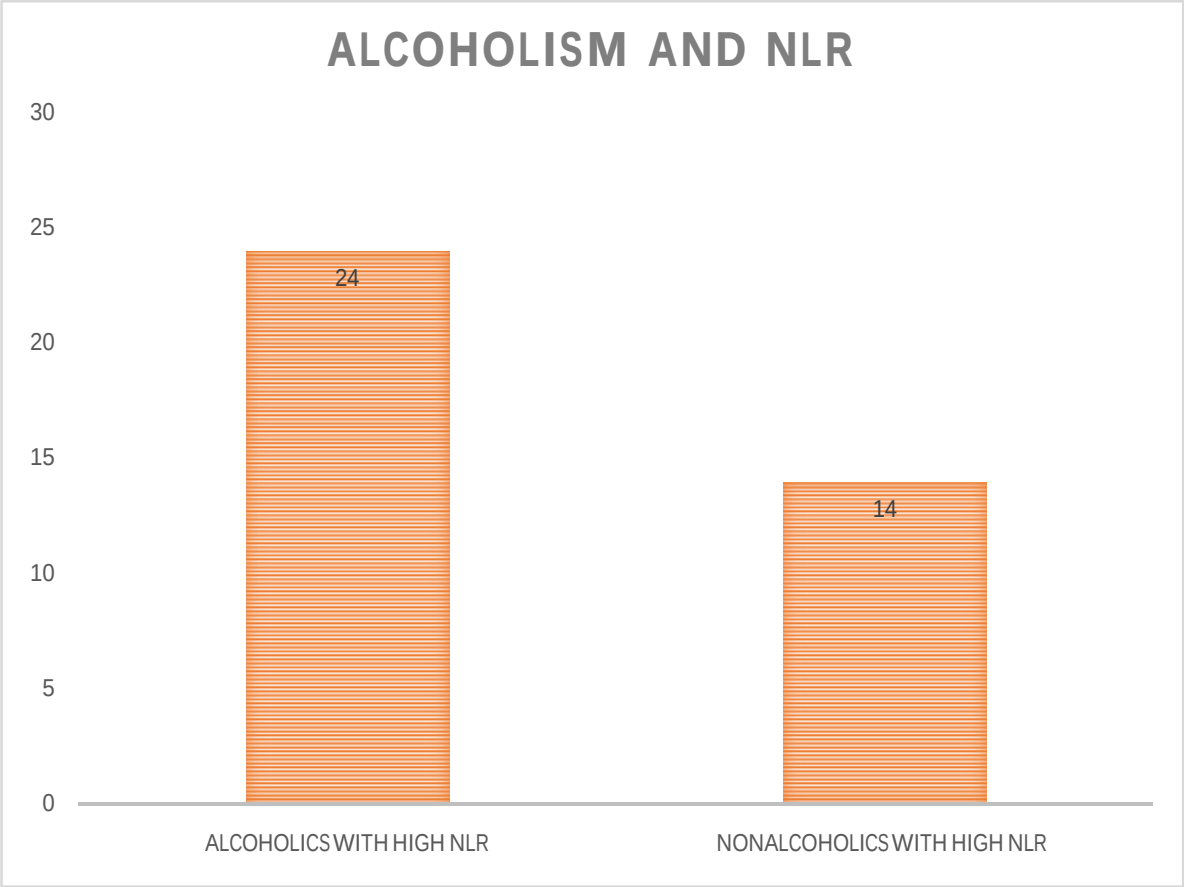
CHART 12 – SEX DISTRIBUTION IN ALCOHOLICS



Alcoholism was more prevalent in the study population. It was more prevalent among the males. Among the Females though the prevalence was very low compared to the males, alcoholism was also found as the cause in a subset of females in the study population.

It is a very significant factor in females because when compared to males females don't tolerate alcoholism and develop cirrhosis, earlier and with comparatively lesser amount of alcohol consumption when compared to males.

CHART 13 – ALCOHOLISM AND NLR



Among the study population, the prevalence of High NLR was studied, that showed a statistically insignificant prevalence of higher NLR among the Alcoholics.

In the study population, the subjects included were already known cases of cirrhosis due to a variety of causes. But in general population, in persons who are not cirrhotics, the prevalence of Higher NLR in Alcoholics when compared non alcoholics need to be studied.

TABLE 8 – ALCOHOLISM AND NLR

	ALCOHOLIC	NON-ALCOHOLIC
TOTAL	72	28
ELEVATED NLR	24	14
NORMAL NLR	48	14

TABLE 9 –CALCULATION OF P VALUE

DIFFERENCE	10%
95% CI	-10.5373 TO 25.3290
CHI-SQUARED	1.195
DF	1
SIGNIFICANCE LEVEL	P = 0.2744

The P value obtained was 0.2744, which is more than 0.05, and so statistically insignicant. Thus Alcoholism is not significantly related to the raised NLR ratio in our study group of patients

DISCUSSION

Liver Cirrhosis is a common end point of various causes of chronic liver diseases. Pathologically cirrhosis liver consists of widespread fibrosis with nodular regeneration. The rate at which chronic liver disease transforms into Hepatic cirrhosis is highly unpredictable and it varies depending upon a lot of factors, the most important of them being the cause of the chronic liver disease.

The survival percentage of patients with cirrhosis declines with the progression of years, for example in one study the survival at the end of one year was 67% and it declined to 11% at ten years.

In patients with compensated stage of Liver cirrhosis the, most common reason for mortality was progression to decompensated state of liver cirrhosis. Development of complications in the form of upper gastrointestinal bleeding, ascites, Hepatic encephalopathy significantly reduces the chances of survival of the cirrhosis patients.

Mortality and survival rates in Cirrhosis patients, despite the state of the disease is also influenced by the associated co-morbid conditions. Presence of Co morbid conditions accelerate the progression of cirrhosis and also the predispose the patients for decompensation which significantly decreases the survival benefit and the mortality rates in the group of patients with co-morbid conditions, when compared to liver cirrhosis patients of the same stage of the disease without complications.

In Indian population, there are a lot of co-morbid conditions, the chief cause among them is alcoholism, among others.

The Rate of transformation of compensated cirrhosis to a decompensated state is highly variable and it mainly depends upon the cause of cirrhosis. For example the rateof progression is slow, around 4% for Hepatitis C virus associated cirrhosis when compared to hepatitis B virus associated cirrhosis, which has a rate of around 10% progression to Decompensated state.

Development of renal failure, concurrent infections of various aetiology, concurrent consumption of alcohol are all associated with rapid progression of compensated liver disease to decompensated liver disease.

So the prevention of progression of compensated liver cirrhosis by effectively management and early identification of such a progression greatly reduces the rate of mortality and increase the survival benefit.

Effective management of compensated liver cirrhosis includes effective management of the causative factor of the cirrhosis. Other measures include screening for the development of oesophageal varices, by upper gastro-intestinal endoscopy periodically, screening for the development of hepatocellular carcinoma every six months, stopping alcoholism, losing weight and life style modification.

All these above said factors make the early prediction of progression of compensated state to decompensated state very important as timely intervention at this state has a significant impact in prevention of the development of a decompensated state and also significantly reduces the mortality rate and improves the survival benefit and duration of survival of compensated liver cirrhosis patients.

Now these things make tools that helps to predict early the progression of compensated to decompensated state. Many such markers are being invented. Neutrophil to lymphocyte ratio is one such tool, that is cheap, easily available and easily reproducible.

Our study is conducted at the Coimbatore medical college Hospital Regarding NLR ratio as a predictor of Prognosis in Liver Cirrhosis Patients.

Samples which were collected from the patients were analysed with strict confidentiality and the results were also kept confidential.

Among the patients studied, the majority [78%] is formed by males. Female form only 22% of the study population. The predominance of male patients in the study can be directly correlated to the higher prevalence of alcoholism in males compared to the females.

Among the study population only 15% is constituted by age group less than 40. A major group of the study population is formed by the age group 40 to 60. As mentioned in various studies cirrhosis affects the important productivephase of an individual. A minor group of patients only fall in an age group of more than 60. As also the prevalence of cirrhosis below the age of 30 in the study population is nil. So from this we can infer cirrhosis except rarely don't occur in the extremes of the age group and it occurs exclusively in the middle aged people from 30 to 60, which is the most productive phase of an individual's career in all aspects, which makes cirrhosis of liver a huge burden both for the society and for the family of the patient.

NLR ratio is calculated from the blood samples collected from the study subjects by dividing the absolute Neutrophil count by the absolute Lymphocyte count. The samples collected were analysed in coulter principle machine cell counter and the total cell count, differential cell count of the WBC were obtained.

The caliberation of the cell counter machines were absolute up-to date and was verified. The samples were processed in the Laboratory of Coimbatore medical college hospital. There was no inter observer variability as the samples were analysed by automated machines.

The NLR ratio normal value is 2.72 as in numerous previous studies involving NLR ratio. The NLR ratio calculated and found out to be higher than the reference value in 38 subjects. In the other 62 patients the NLR ratio is in the normal range.

NLR ratio was less than 2 in 31% of the patients. It was between 2 to 4 in 34% patients. It was more than 4 in 24% of the patients. It was more than 10 in 3% of the patients.

All the 3% patients who had more than 10 value of NLR had more than one complications.

The lowest NLR value in our study population was 1.16 and the highest value was 18.09.

Of the 38 % of patients who had an elevated NLR 32% developed complications in the form of Upper gastrointestinal bleeding, Ascites or Hepatic encephalopathy either in single or in complication.

Of the 62% of the study population who had a normal NLR, only8% developed complications and the rest of 54% didn't develop any complications. The two sample groups were compared and the P value was calculated.

In the calculation, the P value is found to be 0.0021 which is highly significant. This shows us that elevated NLR is associated with higher incidence of complications in cirrhosis patients and is a useful marker in predicting the occurrence of complications in the future.

Alcoholism is highly prevalent among our study subjects, so study was done to see whether there can be alcohol is contributing factor.

The observed P value was 0.2744 which is more than 0.05, and thus is statistically insignificant. So alcoholism doesn't have a significant impact in our study group.

SUMMARY

Liver cirrhosis is one of the leading cause of mortality and morbidity. Liver cirrhosis is due to a variety of reasons of which viral hepatitis and alcoholism are the leading causes in India.

Liver cirrhosis usually occurs in the most productive age group of a person and so adds to significant financial burden to both the family and country. The life expectancy is significantly lower and mortality rate is significantly higher in the decompensated Liver disease compared to compensated liver cirrhosis, which has a better survival rate and less mortality.

The progression of a patient from compensated to decompensated occurs due to a number of factors, the main being the cause of liver disease and the associated co-morbid conditions.

So a marker that can predict the occurrence of decompensated state and complications liken UGI bleed, ascites and HE can help in early identification of such subset of compensated liver cirrhosis patients who are more likely to develop these complications.

Early intervention in this subset of patients can prevent them from progression to a decompensated state and also prevents complication related mortality and improves significantly the life expectancy.

Neutrophil to lymphocyte ratio is a cheap, easily available, less complicated and easily reproducible marker to assess the prognosis of liver cirrhosis patients.

100 selected patients of liver cirrhosis who fulfilled the inclusion and exclusion criteria were included in the study. Blood samples were collected and Neutrophil to lymphocyte ratio was calculated for all subjects and they were followed up for a period of one year.

Among the study subjects 78 were males and 22 were females. Of these 72 were alcoholics and 28 were non-alcoholics.

In the study population 38 subjects had elevated NLR ratio [> 2.72] and 62 had normal NLR ratio [< 2.72].

Among the study population 40 patients developed complications in the form of UGI bleed, ascites and HE either single or in combination.

In the High NLR group of 38 patients 32 developed complications and in Normal NLR group of 62 patients 8 developed complications in the course of the follow up. We analysed the results of the study by chi square test and the p value was less than 0.05 which is statistically very significant.

So we conclude that Blood neutrophil to Lymphocyte ratio is highly significant and can be used as a prognostic marker in liver cirrhosis to detect the likelihood of development of complications and progression from a compensated to a decompensated state.

CONCLUSION

The study that Blood Neutrophil to Lymphocyte ratio as a prognostic marker in Liver cirrhosis patients is conducted in Coimbatore Medical College Hospital in the period of study from July 2015 to June 2016.

The blood sample of 100 cirrhosis patients were collected and analysed for Blood Neutrophil to Lymphocyte ratio.

NLR ratio was calculated and found to be elevated [>2.72] in 38 patients and 62 patients had normal NLR [<2.72]. Out of the 38 patients with elevated NLR 32 developed complications and out of 62 patients with normal NLR 8 patients developed complications.

We subjected the results to statistical analysis which revealed a P value of less than 0.05 which is hugely significant. This study reveals that cirrhosis patients with elevated NLR have a high likelihood of developing complications compared to patients with normal NLR.

So we can infer that Blood Neutrophil to Lymphocyte Ratio is a prognostic marker in Liver Cirrhosis.

BIBLIOGRAPHY

1. 4 CouinaudC .*Le Foie. Etudes Anatomiques et Chirurgicales*. Paris : Masson , 1957

2 Bioulac - Sage P , Lafon ME , Saric J *et al* . Nerves and perisinusoidal cells in human liver . *J. Hepatol.* 1990 ;**10** : 105 – 112 .

3. RoskamsT ,Desmet VJ , Verslype C . Development, structure and function of the liver . In: Burt A D ,Portmann BC , Ferrell LD , eds. *MacSween's Pathology of the Liver* , 5th edn . Edinburgh : Churchill Livingstone Elsevier , 2007 , p. 1

4. Crawford AR , Lin X - Z , Crawford JM. The normal adult human liver biopsy: a quantitative reference standard . *Hepatology* 1998 ;**28** : 323 – 331

5. Rappaport AM. The microcirculatory acinar concept of normal and pathologic hepatic structure . *Beitr. Pathol.* 1976; **157** : 215 – 243

6. SmedsrodB , De Bleser PJ , Braet F *et al* . Cell biology of liver endothelial and Kupffer cells . *Gut* 1994 ;**35** : 1509 – 1516

7. Horn T ,Christoffersen P , Henriksen JH . Alcoholic liver injury: defenestration in noncirrhotic livers. A scanning microscopic study . *Hepatology* 1987 ; **7** : 77 – 82 .

8. RockeyDC ,Weisiger RA . Endothelin induced contractility of stellate cells from normal and cirrhotic rat liver: implications for regulation of portal pressure and resistance . *Hepatology* 1996 ;**24** : 233 – 240

9. KannoN ,LeSage G , Glaser S *et al* . Functional heterogeneity of the intrahepatic biliary epithelium . *Hepatology* 2000 ;**31** : 555 – 561 .

10. Jungermann K , Kietzmann T . Oxygen: modulator of metabolic zonation and disease of the liver . *Hepatology* 2000 ;**31** : 255 – 260

11. Burke ZD , Reed KR , Phesse TJ *et al* . Liver zonation occurs through a β - catenin - dependent, c - Myc - independent mechanism *Gastroenterology* 2009 ;**136** : 2316 – 2324

12. Fausto N. Liver regeneration and repair: hepatocytes, progenitor cells, and stem cells . *Hepatology* 2004 ;**39** : 1477 – 1487

13. Kaplowitz N. Mechansism of liver cell injury .*J. Hepatol.* 2000 ;**32** (Suppl. 1): 39 – 47

14. Lemasters JJ. Dying a thousand deaths: redundant pathways from different organelles to apoptosis and necrosis . *Gastroenterology* 2005 ;**129** : 351 – 360

15. Jaeschke H , Gujral JS , Bajt ML . Apoptosis and necrosis in liver disease . *Liver Int.* 2004 ;**24** : 85 – 89

16. Poynard T , Bedossa T , Opolon P . natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR and DOSVIRC groups .*Lancet* 1987 ;**349** : 825 – 832

17. RockeyDC , Caldwell SH , Goodman ZD *et al.* Liver Biopsy AASLD position paper .*Hepatology* 2009 ;**49** : 1017 – 1044

18. Finn SM , Rowland M , Lawlor F *et al.* The significance of cutaneous spider naevi in children . *Arch. Dis. Child.* 2006 ; **91** : 604 – 605

19. Pirovino M , Linder R , Boss C *et al.* Cutaneous spider nevi in liver cirrhosis: capillary microscopical and hormonal investigations .*Klin. Wochenschr.* 1988 ;**66** : 298 – 302 .

20. Dickinson CJ . The aetiology of clubbing and hypertrophic osteoarthropathy .*Eur. J. Clin. Invest.* 1993 ;**23** : 330 – 338 .

21. EagonPK , Elm MS , Stafford EA *et al.* Androgen receptor in human liver: characterization and quantifi cation in normal and diseased liver . *Hepatology* 1994 ;**19** : 92 – 100

22. Bannister P , Handley T , Chapman C *et al.* Hypogonadism in chronic liver disease: impaired release of luteinizing hormone .*Br. Med. J.* 1986 ;**293** : 1191 – 1193

23. Cundy TF , Butler J , Pope RM *e t al.* Amenorrhoea in women with non - alcoholic chronic liver disease . *Gut* 1991 ;**32** : 202 – 206 .

24. Van denVeldeS ,Nevens F , Van Hee P *et al.* GC- MS analysis of breath odor compounds in liver patients . *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* 2008 ;**875** : 344 – 348 .

25. Kudo M. Riedel ’ s lobe of the liver and its clinical implication *Intern. Med* .2000 ;**39** : 87 – 88

26. Philips DM ,LaBrecque DR , Shirazi SS. Corset liver . *J. Clin. Gastroenterol.* 1985 ;**7** : 361 – 368

27. HadjisNS ,Blumgart LH . Clinical aspects of liver atrophy . *J. Clin. Gastroenterol.* 1989 ;**11** : 3 – 7

28. RadinDR ,Colletti PM , Ralls PW *e t al* . Agenesis of the right lobe of the liver . *Radiology* 1987 ;**164** : 639 – 642

29. den Bergh AAH , Muller P. Uber eine und eineindirekte Diazoreaktion auf Bilirubin .*Biochem. Z.* 1916 ;**77** : 90 .

30. TiribelliC ,Ostrow JD . New concepts in bilirubin and jaundice: report of the Third International Bilirubin Workshop, April 6 – 8, 1995, Trieste, Italy .*Hepatology* 1996 ;**24** : 1296 – 1311

31 Price CP ,Alberti KGMM. Biochemical assessment of liver function . In: Wright R ,Alberti KGMM , Karran S , Millward - Sadler GH , eds. *Liver and Biliary Disease - Pathophysiology, Diagnosis and Managemement*.London :W.B.Saunders , 1979 , p. 381 – 416

32. Whitehead MW , Hawkes ND , Hainsworth I *et al* . A prospective study of the causes of notably raised aspartate aminotransferase of liver origin . *Gut* 1999 ;**45** : 129 – 133

33. Ludwig S ,Kaplowitz N . Effect of serum pyridoxine deficiency on serum and liver transaminases in experimental liver injury in the rat . *Gastroenterology* 1980 ;**79** : 545 – 549

34. Angulo P ,Keach JC , Batts KP *et al* . Independent predictors of liver fi brosis in patients with nonalcoholic steatohepatitis *Hepatology* 1999 ; **30** : 1356 – 1362

35. Weiss MJ , Ray K , Henthorn PS *et al* . Structure of the human liver / bone / kidney alkaline phosphatase gene . *J. Biol. Chem.* 1988 ;**263** : 12002 – 12010 .

36. Maldonado O ,Demasi R , Maldonado Y *et al* . Extremely high levels of alkaline phosphatase in hospitalized patients . *J. Clin. Gastroenterol.* 1998 ;**27** : 342 – 345

37. Cassidy WM , Reynolds TB . Serum lactic acid dehydrogenase in the differential diagnosis of acute hepatocellular

38 .iRegev A , Berho M , Jeffers LJ *et al.* Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection . *Am. J. Gastroenterol.* 2002 ;**97** : 2614 – 2618njury .*J. Clin. Gastroenterol.* 1994 ;**19** : 118 – 121 .

39. BlomleyM , Lim A , Harvey C *et al.* Liver microbubble transit time compared with histology and Child - Pugh score in diffuse liver disease. A cross sectional study .*Gut* 2003 ; **52** : 1188 – 1193

40. RockeyD , Bissell D . Noninvasive measures of liver fi brosis . *Hepatology* 2006 ;**43** : S113 – S20

41. Forbes SJ , Russo FP , Rey V *et al.* A significant proportion of myofibroblasts are of bone marrow origin in human liver fibrosis .*Gastroenterology* 2004 ;**126** : 955 – 963.

42. RockeyDC , Caldwell SH , Goodman ZD *et al.* Liver Biopsy:

43. AAScheuerPJ ,Lefkowitch JH . *Liver Biopsy Interpretation* , 7th edn . Elsevier Saunders , 2006 , p. 171SLD position paper . *Hepatology* 2009 ;**49** : 1017 – 1044

44. PoynardT ,Bedossa T , Opolon P . natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR and DOSVIRC groups .*Lancet* 1987 ;**349** : 825 – 832

45. Hammel P CA , O ' Toole D , Ratouis A *et al.* Regression of liver fi brosis after biliary drainage in patients with chronic pancreatitis and stenosis of the common bile duct . *N. Eng. J. Med.* 2001 ;**344** : 418 – 423

46. Dixon JB ,Bhathal PS , Hughes NR *et al.* Nonalcoholic fatty liver disease: improvement in liver histological analysis with weight loss . *Hepatology* 2004 ;**39** : 1647 – 1654

47. George SL , Bacon BR , Kusal L *et al.* Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5 - year follow - up of 150 patients . *Hepatology* 2009 ; **49** : 729 – 738

48. GinesP , Quintero E , Arroyo V *et al.* Compensated cirrhosis: natural history and prognostic factors . *Hepatology* 1987 ;**7** : 122 – 128 .

49. CarithersRL ,Herlong HF , Diehl AM *et al.* Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicentertrial *.Ann. Intern. Med.* 1989 ;**110** : 685 – 690 .

50. Newell GC . Cirrhotic glomerulonephritis: incidence, morphology, clinical features, and pathogenesis . *Am. J. Kidney Dis.* 1987 ;**9** : 183 – 190

51. Noble - Jamieson G , Thiru S , Johnston P *et al.* Glomerulonephritis with end - stage liver disease in childhood *Lancet* 1992 ;**339** : 706 – 707 .

52. Van denVeldeS ,Nevens F , Van Hee P *et al.* GC- MS analysis of breath odor compounds in liver patients . *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* 2008 ;**875** : 344 – 348.

53. WeissenbornK . Diagnosis of encephalopathy .*Digestion* 1998 ;**59** (Suppl. 2): 22 – 24

54. FerenciP , Lockwood A , Mullen K *et al.* Hepatic encephalopathy – definition, nomenclature, diagnosis, and quantifi cation: Final report of the working party

at the 11th World Congresses of Gastroenterology, Vienna, 1998 . *Hepatology* 2002 ;**35** : 716 – 721 .

55. MontagneseS , Middleton B , Skene D *et al.* Night – time sleep disturbance does not correlate with neuropsychiatric impairment in patients with cirrhosis . *Liver Int.* 2009 ;**29** :

56. SchomerusH , Hamster W . Neuropsychological aspects of portal – systemic encephalopathy . *Metab. Brain. Dis.* 1998 ; **13** : 361 – 377

57. Parsons - Smith BG ,Summerskill WHJ , Dawson AM *et al.* The electroencephalograph in liver disease .*Lancet* 1957; **2** : 867 – 871 .

58. MontagneseS ,Amodio P , Morgan MY . Methods for diagnosing hepatic encephalopathy in patients with cirrhosis: a multidimensional approach . *Metab. Brain Dis.* 2004 ;**19** : 281 – 312

59. BerdingG ,Banati RB , Buchert R *et al.* Radiotracer imaging studies in hepatic encephalopathy: ISHEN practice guidelines *Liver Int.* 2009 ;**29** : 621 – 628 .

60. Kramer L ,Tribl B , Gendo A *et al.* Partial pressure of ammonia versus ammonia in hepatic encephalopathy . *Hepatology* 2000 ;**31** : 30 – 34 .

61. HouraniBT ,Hamilin EM , Reynolds TB . Cerebrospinal fluid glutamine as a measure of hepatic encephalopathy . *Arch. Intern. Med.* 1971 ;**127** : 1033 – 1036

PROFORMA

1. NAME :

2. AGE :

3. SEX :

4. WHETHER PATIENT IS ON :

   CYTOTOXIC DRUGS

5. WHETHER PATIENT IS ON :

   CORTICOSTEROIDS

6. WHETHER PATIENT IS SUFFERING :

   FROM FEVER FOR THE 2 WEEKS OR

   ANY OTHER SYMPTOM OF INFECTION

7. WHETHER KNOWN CASE OF :

   HEPATOCELLULAR CARCINOMA

8. WHETHER KNOWN CASE HIV OR ANY :

   OTHER SECONDARY

IMMUNODEFICIENCY

9. WHETHER THE PATIENT IS PREGNANT :

OR LACTATING

10. WHETHER THE PATIENT IS AN ALCOHOLIC :

11. WHETHER CONSENT IS TAKEN :

12. WHETHER BLOOD SAMPLES COLLECTED :

13. ABSOLUTE NEUTROPHIL COUNT :

14. ABSOLUTE LYMPHOCYTE COUNT :

15. NEUTROPHIL TO LYMPHOCYTE RATIO :

16. FINAL INTERPRETATION :

CONSENT FORM

Yourself Mr./Mrs./Ms……..are being asked to be a Participant in the research study titled — Blood Neutrophil to Lymphocyte ratio as a Prognostic marker in Liver Cirrhosis Patients. CMC Hospital, Coimbatore, conducted by DR.K.S.DAKSHINAMOORTHY., Post Graduate Student, Department of General Medicine, Coimbatore Medical College. You are eligible after looking into the inclusion criteria. You can ask any question you may have before agreeing to participate.

PURPOSE OF RESEARCH:

The aim of the study is to evaluate the role of NLR as a prognostic marker in Patients with stable liver cirrhosis

To identify early, the group of stable cirrhotic patients with likelihood of developing complications in the near future.

PROCEDURES INVOLVED:

Collection of blood from the patients for NLR calculation.

RESEARCH BEING DONE:

Blood Neutrophil to Lymphocyte ratio as a Prognostic marker in Liver Cirrhosis Patients.

DECLINE FROM PARTICIPATION:

You have the option to decline from participation in the study existing protocol for your condition.

PRIVACY AND CONFIDENTIALITY:

Privacy of individuals will be respected and any information about you or provided by you during the study will be kept strictly confidential..

AUTHORIZATION TO PUBLISH RESULTS:

Results of the study may be published for scientific purposes and/or presented to scientific groups, however you will not be identified.

STATEMENT OF CONSENT

I volunteer and consent to participate in this study. I have read the consent or it has been read to me. The study has been fully explained to me, and I may ask questions at anytime.

---------- ----------

Signature /Left thumb impression Date

(volunteer)

---------- ----------

Signature of witness Date

MASTER CHART

S.No	Name	Age	Sex	Total Count *10^3	Neutrophil Count %	Lymphocyte Count %	NLR	UGI BLEED	Ascites	HE	Alcoholism	
1.	Thayammal	47	F	12.6	55.4	23.2	2.38				+	
2.	Krishnan	50	M	11.2	85.5	7.3	11.71	+	+		+	
3.	Avudaiyappan	52	M	5.5	56.8	26.4	2.151				+	
4.	Bose	50	M	6.4	60.3	31.2	1.93	+			+	
5.	Venkatesh	52	M	4.6	52.1	26.2	1.98					
6.	Thiruman	49	M	5	83.8	6.2	13.51		+	+	+	
7.	Saraswathi	37	F	7.8	51.6	23.8	2.18		+			
8.	Chinnan	6o	M	6.5	55.4	34.8	2.23				+	
9.	Narayanan	52	M	9.5	82.1	11.6	7.077					
10.	Alex	46	M	11.7	81.2	12.6	6.44				+	
11.	Muniyammal	58	F	4.6	57.4	22.5	2.55					
12.	Murugaperumal	62	M	5.7	58.5	24.3	2.40				+	
13.	Kalyanasundaram	42	M	5.4	81.0	11.3	7.168	+	+		+	
14.	Karuppasamy	46	M	6.8	78.9	9.4	8.39		+	+	+	
15.	Palanivel	48	M	7.1	73.2	45.6	1.60				+	

16.	Swetha	39	F	8.6	71.2	36.5	1.95					
17.	Arumugam	49	M	5.8	69.3	20.9	3.3157			+	+	
18.	Aiyavu	42	M	9.5	78.7	17.1	4.602				+	
19.	Velmurugan	44	M	6.8	72.4	32.3	2.24				+	
20.	Ganapathy	56	M	10.6	77.5	37.6	2.06	+	+		+	
21.	Perumal	62	M	5.9	76.4	44.6	1.61					
22.	Murugan	56	M	9.4	78.2	13.0	6.01	+		+	+	
23.	Abdul Razzak	46	M	6.4	74.5	39.2	1.90				+	
24.	Lakshmi	55	F	7.6	75.2	41.9	1.79				+	
25.	Priya	37	F	8.8	73.1	21.0	3.48	+	+			
26.	Deivanathan	49	M	10.8	79.7	36.8	2.165				+	
27.	Krishnamoorthy	54	M	11.6	69.6	23.4	2.97					
28.	Palaniyappan	53	M	7.8	64.3	34.3	1.87				+	
29.	Nallayaian	59	M	6.6	68.2	14.7	4.65		+		+	
30.	Praveen	36	M	8.9	63.5	29.6	2.14				+	
31.	Mohammed Shiek	52	M	8.3	59.9	21.9	2.735			+	+	
32.	Elumalai	68	M	4.7	62.7	28.5	2.2		+		+	
33.	Saravaanan	33	M	5.9	65.8	33.6	1.95				+	

34.	Palani	62	M	11.8	92.3	5.1	18.09	+	+		+	
35.	Antony	70	M	6.8	61.5	39.7	1.54				+	
36.	Samuel	46	M	7.6	67.8	39.7	1.70				+	
37.	Raja	51	M	8.3	70.1	15.2	4.61		+		+	
38.	Kaliathal	41	F	10.7	66.2	29.8	2.22					
39.	Karupu	53	M	4.8	62.1	17.7	3.50				+	
40.	Parvathy	64	F	5.9	43.8	41.5	1.055					
41.	Paramasivan	56	M	4.9	49.5	36.2	1.362				+	
42.	Kaliyappan	42	M	11.8	84.0	10.7	7.85		+	+	+	
43.	Praveen	36	M	5.7	48.5	29.4	1.64				+	
44.	Mohammed Ali	61	M	5.6	47.5	36.8	1.290				+	
45.	George	69	M	4.8	78.9	14.4	5.47		+		+	
46.	Kannagi	64	F	8.6	59.2	20.6	2.87		+			
47.	Stephen	37	M	7.0	48.5	38.2	1.26				+	
48.	Arivalaghan	56	M	5.9	78.6	9.9	7.93	+	+		+	
49.	Meena	48	F	6.7	45.8	36.2	1.26					
50.	Kannappan	46	M	7.3	41.8	28.4	1.471				+	
51.	Anandakumar	54	M	8.1	73	11.3	6.46		+	+		

52.	Siluvairaj	59	M	10.7	49.8	29.4	1.69				+	
53.	Siva	40	M	6.9	75.7	14.2	5.3	+			+	
54.	Jose	67	M	7.1	55.4	17.5	3.16				+	
55.	Tamilarasan	55	M	9.2	56.3	29.8	1.889				+	
56.	Velmurugan	41	M	10.1	59.8	27.8	2.15				+	
57.	Vellaiyan	49	M	5.9	58.4	29.4	1.98	+			+	
58.	Mohammed Rafique	57	M	6.3	69.2	18.4	3.76				+	
59.	Haseena	49	F	8.4	55.26	35.12	1.57					
60.	Lilly	53	F	7.9	53.29	32.62	1.633		+		+	
61.	Sanjeevi	55	M	4.9	57.25	28.5	2.08				+	
62.	Prakash	33	M	8.3	60.82	30.12	2.019				+	
63.	Zaheer Hussain	49	M	6.2	72.6	13.O	5.58	+	+			
64.	Mariammal	60	F	4.7	54.18	27.4	1.97				+	
65.	Selvakumar	37	M	5.7	75.2	17.6	4.25	+	+			
66.	Kannappan	46	M	6.8	65.3	28.9	2.259				+	
67.	Fathima	56	F	4.9	64.3	16.4	3.92	+		+		
68.	Petchiyammal	68	M	11.7	68.7	29.8	2.3O					

69.	Murugappan	70	M	10.5	67.52	28.74	2.34				+	
70.	Nallasamy	65	M	5.8	82.9	11.8	7.02	+		+	+	
71.	Chellathai	56	F	6.7	67.46	26.23	2.571					
72.	Chandiran	49	M	7.3	84.2	8.9	9.4		+	+		
73.	Prabhu	31	M	5.7	67.1	18.6	3.6	+	+		+	
74.	Rajkumar	62	M	5,9	63.12	35.6	1.77				+	
75.	Chinnathai	65	F	9.7	62.1	8.4	7.35					
76.	Veeran	57	M	6.2	66.73	25.2	2.64	+	+		+	
77.	Vetrivel	41	M	4.8	66.3	16.2	4.09		+	+		
78.	Paraman	57	M	6.4	74.8	41.2	1.81				+	
79.	Kumutha	64	F	8.5	79.0	40.5	1.95		+	+		
80.	Packianathan	46	M	9.3	72.3	18.4	3.92				+	
81.	Vinoth	34	M	11.3	76.2	37.5	2.03				+	
82.	Manoharan	48	M	8.6	74.2	31.2	2.378					
83.	Annammal	60	F	7.5	76.5	16.5	4.69	+	+			
84.	Catherine	56	F	5.8	77.8	30.5	2.55					
85.	Suryakumar	39	M	6.2	74.6	35.8	2.08				+	
86.	Veeraiyammal	52	F	4.8	72.6	19.2	3.78		+	+		

87.	Kaliammal	59	F	9.6	78.31	29.81	2.626					
88.	Chelladurai	63	M	8.0	79.52	30.57	2.601				+	
89.	Subash	36	M	11.8	81.2	17.3	4.69	+	+		+	
90.	Ponnan	60	M	5.8	45.61	32.14	1.419					
91.	Periyanayagi	49	F	11.8	47.27	24.12	1.959					
92.	Marrappan	61	M	10.5	42.15	20.14	2.09	+			+	
93.	Dhawoodali	56	M	6.4	46.78	22.98	2.03				+	
94.	Mohan	44	M	7.3	43.23	21.7	2.02				+	
95.	Johnson	55	M	11.9	66.8	15.2	4.39	+	+		+	
96.	Aishwarya	46	F	10.7	42.23	20.54	2.055					
97.	Periyasamy	53	M	5.7	47.58	32.44	1.48					
98.	Karupathal	65	F	11.1	60.5	14.3	4.2	+	+			
99.	Thirupathi	61	M	10.2	48.17	41.25	1.16					
100.	Packianathan	35	M	4.6	74.7	39.6	1.88					